

POSTER SESSION 2

Monday, March 7, 2005

8:30 AM–5:00 PM

Poster numbers 188–383

Authors present: 12:30 PM–2:15 PM

OTHER CLINICAL

P188

Prophylactic treatment of migraine with botulinum toxin A in Koreans: An open-label study

M.Y. Park, K.Y. Ahn (Daegu, Kyungbuk, South Korea)

Background: The prevalence rate of migraine is 10% in women and 3% in men in general population of Korea. However, more people suffer from migraine without getting precise diagnosis. Prophylactic and abortive therapeutic regimens for migraine have limitations in their efficacy and have many side effects. But botulinum toxin may be effective in the prevention of migraine for a long term period.

Objectives: To evaluate prospectively the effect of botulinum toxin type A injection on the frequency and severity of migraine in Koreans.

Methods: Nineteen patients (12 women, 7 men) with migraine (8 migraine with aura, 11 migraine without aura) according to HIS criteria were enrolled in the study.

The frequency (number of migraine per month) and intensity (recorded on an analog scale of 1 to 10, 10 being most severe) of headache and subjective GAI scale (global assessment of improvement) were recorded before and after treatment.

Forty-eight units of Botox® were injected into bilateral corrugator supercilli, temporalis, and frontalis muscles.

Results: At 1 months, 14 (74%) of 19 patients experienced significant improvement of GAI scale (more than 50%, $P < 0.05$, duration 6.0 months). Four patients (21%) reported complete elimination of headache ($P < 0.05$, duration, 5.5 months). Two patients (10%) did not notice a change in headache. Overall, headache frequency decreased from 19 to 10 per month on average ($P < 0.05$), and the intensity decreased from 10 to 4 ($P < 0.001$). Six patients (75%) reported complete elimination of aura. Eleven patients (58%) experienced complete elimination of associated gastrointestinal symptoms and 8 patients (42%) reported significant improvement of associated gastrointestinal symptoms ($P < 0.001$). Two patients (10%) reported minor side effects. The duration of efficacy of botulinum toxin type A injections was 5.7 ± 1.4 months on average.

Conclusions: Prophylactic treatment for migraine using botulinum toxin type A is safe and effective to reduce frequency and severity of paroxysmal migraine attacks and associated symptoms in Koreans.

P189

Paroxysmal nonkinesigenic dyskinesia responsive to a gluten-free diet

D.A. Hall, J. Parsons, M.A. Leehey, T.A. Benke (Denver, Colorado, USA)

Objective: To describe paroxysmal nonkinesigenic dyskinesia (PNKD) responsive to a gluten-free diet in a child with biopsy proven celiac disease.

Background: Neurological signs and symptoms associated with celiac disease have been recently described in the literature and encompass a wide range of movement disorders, including cerebellar ataxia, myoclonus, and chorea. PNKD has not previously been reported in associated with celiac disease.

Methods: A child with PNKD was followed for 6 years by pediatric neurologists and movement disorder specialists.

Results: The episodes began at the age of 6 months are described as twisting of her upper body to one side with an outstretched arm and a

flexed position of the left leg. The episodes would occur 10–20 times per day and would wax and wane in frequency. She was treated with carbamazepine, gabapentin, acetazolamide, phenytoin, clonazepam, and levodopa/carbidopa without relief of her symptoms. At the age of 8, she had an acute gastrointestinal illness and IgA antigliadin antibodies were positive. The patient was referred to gastroenterology and bowel biopsy was performed, showing evidence of celiac disease. After starting a gluten-free diet, the episodes decreased in frequency, and she has now been without symptoms for 6 months.

Conclusions: PNKD may be another movement disorder that is associated with celiac disease. Celiac disease is thought to be autoimmune due to the presence of several different immunoglobulin A antibodies in affected patients. Neurological syndromes, including cerebellar ataxia, hypotonia, developmental delay, and headache, have an incidence of 10% in children with celiac disease and usually do not improve on a gluten-free diet. Linkage studies of families with PNKD have shown a locus on 2q that may be responsible for classical PNKD and the disorder has been described to improve as children get older. Although it may be difficult to reconcile the likely genetic basis of PNKD with autoimmune celiac disease, the improvement of this child's episodes were temporally related to the initiation of a gluten-free diet. The case report suggests additional studies may be warranted looking at the association of these two disorders and response to a gluten-free diet in other children.

P190

Management of the extrapyramidal syndrome in acquired chronic hepatocerebral degeneration (ACHD)

S. Papapetropoulos, C. Singer (Miami, Florida, USA)

Objectives: To describe the clinical characteristics and therapeutic interventions in a case of Acquired Chronic Hepatocerebral Degeneration (ACHD).

Background: ACHD was first described in 1965 by Victor et al., who intended to make a clear distinction from the "familial type" seen in Wilson disease. The clinical spectrum of ACHD is well defined and includes a predominantly hyperkinetic extrapyramidal syndrome, neuropsychiatric symptoms, or both. Although some evidence about the pathophysiology of ACHD has derived from neuropathological and neuroradiological studies many questions about the current treatment options remain unanswered.

Methods: We describe the clinical characteristics and therapeutic interventions in a patient, who developed ACHD secondary to end-stage liver disease from Hepatitis C. The patient was diagnosed and followed up in the Department of Neurology, University of Miami, School of Medicine.

Results: A 69-year-old female was referred to our Department for the first time 8 years ago for evaluation of her oro-bucco-lingual (OBL) dyskinesias in the setting of hepatic failure caused by Hepatitis C. The OBL dyskinesias have appeared briefly before the patient received a successful liver transplantation. The involuntary movements disappeared post-transplantation only to reappear 3 months later.

Neurological examination revealed, moderate OBL dyskinesias, mild bilateral symmetrical postural hand tremor, asymmetrical (right > left) mild limb and neck rigidity, bradykinesia and postural instability. The patient could only ambulate with assistance. There were no signs of pyramidal, sensory or cerebellar dysfunction.

After trials with haloperidol and benztropine (discontinued due to adverse effects), the patient was gradually started on tetrabenazine (75 mg/day), with almost complete suppression of the OBL dyskinesias. Parkinsonian symptoms caused by tetrabenazine were successfully managed with the addition of a dopamine agonist (DA) (ropinirole 1 mg/day). The patient has remained stable on this combination for the past 2.5 years, with no OBL involuntary movements, and only mild bradykinesia and limb rigidity bilaterally.

Conclusions: We report for the first time the successful combination of tetrabenazine and a DA in the treatment of an extrapyramidal syndrome of hyperkinetic and parkinsonian features cause by ACHD.

P191**Pramipexole is effective in the treatment of restless legs syndrome (RLS): Results of a 6 week, multi-centre, double-blind, and placebo-controlled study**

W. Oertel, K. Stiasny-Kolster (Marburg, Germany)

Objective: To evaluate efficacy and safety of pramipexole in RLS patients over a 6-week treatment period.

Background: Pramipexole, a non-ergot dopamine agonist, has shown to improve RLS symptoms in a small, placebo-controlled, randomised trial in RLS patients by Montplaisir et al. This has been confirmed recently in a large polysomnographic, fixed dose study in RLS patients by Partinen et al.¹. The new study was designed to evaluate efficacy and safety of pramipexole in a large population in a clinical setting over a 6-week treatment period.

Methods: In this 6-week, double-blind, placebo controlled, flexible dose study, patients of at least 18 years of age with idiopathic RLS were randomised to treatment with pramipexole or placebo. Patients underwent a flexible dose titration phase during weeks 1 to 4 (dose range: 0.125–0.75 mg/QD). Patients were on stable doses for at least 2 weeks until week 6. This study had two primary end points. The first was the mean change from baseline to week 6 in the international RLS rating scale of severity (RLSRS) and responder status using Clinical Global Impressions–Improvement (CGI-I) scale score at week 6. An ANCOVA analysis was performed for the RLS rating scale with covariates baseline and age, while CGI-I was analysed with a Mantel-Haenszel test stratified by centre.

Results: A total of 345 patients (from 37 participating centres) received treatment. The mean improvement in the RLSRS total score at week 6 was significantly greater for the pramipexole group compared to the placebo group (adjusted mean change from baseline -12.4 [SE = 0.6] versus -5.8 [SE = 0.9]), $P < 0.0001$. Moreover, 64.4% of the pramipexole treated patients were CGI-I responders (much/very much improved) at week 6 compared to 34.3% of the placebo patients, $P < 0.0001$. Most frequent reported adverse events under pramipexole were headache (13%), nausea (12.2%), and fatigue (9.1%).

Conclusion: In the largest clinical study in RLS patients conducted so far pramipexole showed statistically significant superiority in both primary end points (RLS rating scale and CGI-I) compared to placebo. In addition pramipexole was generally well tolerated.

Reference

1. Partinen et al. AAN abstract. 2004.

P192**Procedimental analyses in movement disorders trials: New approaches in methodological issues**

S.G. Echebarria (Spain)

Introduction: In recent years, a lot of arguments about whether a simple large randomized trial is better than a meta-analysis of small trials in different movement disorders fields have been performed.

Assess agreement between calibrated measurement scores and observed scores in, as an example, cell therapy trials, concerning Relative Validity (RV) in discriminating among group Intraclass Correlation (ICC), evaluates the variability of meta-analyses.

Aim: develop procedures to assess the degree to which procedures in inclusion and exclusion criteria in cell therapy trials are analysed and the way in which data are gathered to provide the knowledge-base to try and answer phase III and IV outcomes in randomized trials.

Methods: It is feasible to use software-based dynamic assessment to measure trial projections and hypotheses (EXPERIPLAN).

To ensure backwards comparability and to facilitate interpretations of results, we need the ability to express the trials scores in the metrics of the usual scales.

Results/Conclusions: Considering logic characteristics of the hypothesis and methodological properties on involved variables in studies, it is possible to offer theoretical knowledge and suggestions in variable control, adding categorial classifications to trial validations.

P193**24-Hour relief of restless legs syndrome (RLS) symptoms with once daily pramipexole**

B. Hognl, W. Poewe (Innsbruck, Austria)

Objective: To evaluate whether pramipexole is effective on RLS severity during the night as well as during the day.

Background: RLS symptoms mostly occur in the evening when patients intend to rest or are going to bed. The beneficial effect of pramipexole on RLS symptoms during the course of the night was shown by one small placebo-controlled crossover trial by Montplaisir et al. However, some patients also suffer from RLS symptoms over the course of the day. Given the half-life of pramipexole of 8–9 h, it is important for patients and physicians to know if a once daily dosing regimen is able to alleviate symptoms over a 24-h period.

Method: In a large-scale randomised, double-blind, placebo-controlled, multi-centre trial in Europe, 345 patients were treated with either pramipexole or placebo in a 2:1 relation. Planned duration of treatment was 6 weeks including a titration phase of up to 4 weeks. Patients rated their severity of RLS symptoms during the night and the day on a Visual Analogue Scale (VAS). This scale measures RLS severity on a continuous 10-cm axis ranging from absent (0) to severe (10), respectively, during the night and during the day. Data could be analysed from 217 patients with pramipexole and 107 with placebo. An ANCOVA analysis was performed in both VAS parameters for the change from baseline with the covariates baseline and age.

Results: The severity of RLS in the course of the night was decreased statistically significant in the pramipexole group compared to placebo (adjusted mean change from baseline -32.5 [SE = 2.0] vs. -12.5 [SE = 2.8]), $P < 0.0001$. In addition the RLS severity during the course of the day was decreased significantly under treatment with pramipexole compared to placebo after the 6 week treatment period (adjusted mean change from baseline -11.9 [SE = 1.5] vs. -1.1 [SE = 2.1]), $P < 0.0001$.

Conclusion: Symptom relief during the course of the night as assessed by VAS confirmed the outcome of the RLS Severity Scale in the large polysomnographic study by Partinen et al. Additionally, the results of our investigation show that pramipexole improves the RLS symptoms during the course of the day too. A once-daily dose regimen with pramipexole is able to improve RLS symptoms over a 24-h time span, suggesting that the therapeutic effect is not directly linked to the pharmacokinetic profile of the compound.

P194**Early and persistent effect of pramipexole in restless legs syndrome (RLS) patients already with the starting dose**

W. Oertel, K. Stiasny-Kolster (Marburg, Germany)

Objective: To evaluate the onset of action of pramipexole in RLS patients.

Background: Pramipexole is a non-ergot dopamine agonist widely used in the treatment of Parkinson's disease. Following a first observation that the drug may be effective in RLS based on a small placebo-controlled cross-over trial by Montplaisir et al., the results of a large polysomnographic dose range finding study by Partinen et al. recently confirmed pramipexoles efficacy in RLS. This new large randomised, double-blind, multi-centre trial conducted in 5 European countries measured the effect of pramipexole after 6 weeks of treatment and showed statistically significant separation from placebo using as primary endpoints the RLS rating scale for severity and Clinical Global Impression-Improvement.

Methods: In addition to the primary endpoint assessed in the study of Partinen et al., which were measured only at baseline and end of study, Patient Global Impression (PGI) was measured weekly and used as basis for the physician's decision whether to up titrate the patient. In order to determine onset and persistence of effect, we analysed the time at which the PGI was first considered much improved or very much improved under treatment. The comparison between pramipexole and placebo was performed with a Cochran-Mantel-Haenszel test stratified by centre.

Results: 31.2% of patients treated with pramipexole showed a PGI response much improved or very much improved already after 1 week on 0.125 mg/d, compared to only 7.5% under placebo treatment ($P < 0.0001$). Moreover, the percentage of patients who showed an initial response and also experienced a persistent response up to week 6 with pramipexole was significantly higher compared to those patients treated with placebo only (19.8% vs. 3.74%; $P = 0.0004$).

Conclusion: Pramipexole showed already a statistically significant effect after 1 week treatment compared to placebo. This response persisted in a significantly larger number of patients up to week 6 compared to placebo. This is important for patients and physicians as they can expect both a fast onset of action as well as a persistent response when treating RLS with pramipexole already with the starting dose of 0.125 mg.

P195

Pramipexole—An effective treatment option in restless legs syndrome (RLS) patients with depressed mood

K. Stiasny-Kolster, W. Oertel (Marburg, Germany)

Objective: To evaluate whether pramipexole is able to influence depressed mood in RLS patients after a 6-week treatment period.

Background: Beside the well-known sensori-motor symptoms of RLS, depressed mood seems to have a relevant prevalence in this patient group.

Methods: In a 6-week, double-blind, placebo-controlled study, patients aged at least 18 years with idiopathic RLS were randomised to treatment with pramipexole or placebo (2:1). Patients underwent an unforced dose titration phase during weeks 1 to 4 (dose range: 0.125–0.75 mg/per day). Patients were on stable doses for at least 2 weeks until week 6. The international RLS rating scale of severity (IRLS) consists of 10 different subitems. Item 10 asks the patient about the severity of the mood disturbances due to the RLS symptoms on a scale ranging from 0 = none, up to 4 = very severe. We analysed the shift of the severity of mood disturbance from baseline to week 6 in the two treatment groups.

Results: A total of 345 patients (37 centres from 5 European countries) received treatment. 217 patients on pramipexole and 107 patients on placebo had baseline and final visit values. 20 patients on placebo (19%) and 39 on pramipexole (18%) had a severe mood disturbance due to their RLS symptoms at baseline. After the 6-weeks treatment significantly more patients treated with pramipexole improved and had none or only a mild mood disturbance 31/39 (79%) compared to 7/20 (35%) treated with placebo (Fisher's-Exact Test, $P = 0.0009$).

Conclusion: Pramipexole has already shown antidepressive properties in Parkinson's disease. This is the first time that these properties could be confirmed in the field of RLS. Depressed mood has a high impact on the decreased quality of life in RLS patients. Moreover most antidepressive drugs even worsen RLS symptoms. So it is of utmost importance that with pramipexole a treatment is available that combines beneficial effects on both, the sensorimotor symptoms and depressed mood in RLS patients.

P196

Pramipexole significantly improves sleep in patients with restless legs syndrome (RLS)

B. Hogl, W. Poewe (Innsbruck, Austria)

Objective: To evaluate the effect of pramipexole on RLS severity at sleep onset and satisfaction with sleep in RLS patients after a 6-week treatment.

Background: Sleep disturbance is one of the main features of RLS. For many RLS patients sleep problems are the first reason to contact their physician. Sleep is interrupted mainly due to the periodic leg movements which can be observed in 80–90% of RLS patients.¹ Drug treatment in patients suffering from RLS should therefore be able to improve the odd feelings in the legs while resting, and should also improve sleep quality.

Methods: In a large placebo-controlled, double-blind, multi-centre trial in Europe, 345 patients were treated for 6 weeks with pramipexole ($n = 230$) or placebo ($n = 115$).

Patients rated their severity of RLS symptoms at the time of getting to sleep as well as their satisfaction with sleep the following morning, both at

baseline and at week 6, with the help of a visual analogue scale. This scale measures RLS severity on a continuous 10-cm axis ranging from absent (0) to severe (10) at sleep onset and satisfaction with sleep. An ANCOVA analysis was performed in both VAS parameters for the change from baseline with covariates baseline and age.

Results: After 6 weeks patients treated with pramipexole had a significantly reduced severity of their RLS symptoms while getting to sleep compared to placebo (adjusted mean change from baseline -31.1 [SE = 2.0] vs. -13.8 [SE = 2.8]), $P < 0.0001$. In parallel, the satisfaction with sleep was statistically significant higher in the pramipexole treated patient group compared to placebo (adjusted mean change from baseline -30.0 [SE = 2.2] vs. placebo -13.3 [SE = 3.1]).

Conclusion: Pramipexole significantly reduces the RLS severity of patients while getting to sleep which is the most critical time point for the occurrence of RLS symptoms. Satisfaction with sleep is also significantly improved in patients suffering from RLS being treated with pramipexole. This result supports the beneficial effect of pramipexole in the treatment of RLS.

Reference

1. Trenkwalder et al., 1996.

P197

Prospective characterization of movement disorders in the Manhattan HIV brain bank project

W. Tse, L. Estanislao, D. Polowitzky, S. Verma, S. Morgello (New York, New York, USA)

Objective: To prospectively characterize the presence of movement disorders in a population of patients with HIV infection.

Background: Despite known extensive basal ganglia involvement in patients with HIV infection, minimal data exists regarding characterization of movement disorders in this population, which have been previously reported in 2–3% of such patients. We studied the prevalence of movement disorders in a group of patients participating in the Manhattan HIV Brain Bank project.

Methods: Patients with advanced HIV disease participating in the Manhattan HIV Brain Bank research project (MBB) were prospectively examined by a movement disorder specialist for the presence of a movement disorder. The MBB is one of the centers of the National NeuroAIDS Tissue Consortium, which provides well-characterized central and peripheral nervous system tissues from HIV-positive patients. Information was also collected regarding patient's age, race, medications, past medical history, CD4 count, and HIV viral load.

Results: Fifty patients (32 males and 18 females, mean age 48 years) were examined. movement disorders were seen in 15/50 (30%) patients, and the mean motor UPDRS score was 3.32 (SD 7.41). The mean CD4 count was 392 cells/mm³ in 47 patients. Twelve patients (24%) had tremor (postural and action-related). Etiologies identified included HIV-related cerebellar degeneration diagnosed by brain biopsy ($n = 1$), PML ($n = 2$), metabolic abnormalities ($n = 2$) and drug-induced ($n = 3$). One of the patients with drug-induced tremors had parkinsonism probably secondary to molindone hydrochloride use. Etiology was unknown in 4 cases, although 2 had a family history of tremor, suggesting the possibility of essential tremor. Two patients (4%) had chorea: one with progressive multifocal leukoencephalopathy (PML) diagnosed by brain biopsy, and the second had multiple cerebral lesions consistent with toxoplasmosis on CT scan that responded to anti-toxoplasmosis regimen. One patient (2%) had myoclonus of unknown etiology. No dystonia was identified.

Conclusion: These data suggest that when specifically evaluated, movement disorders are commonly present in HIV-positive individuals.

P198

Saccadic eye movements: A useful clinical biomarker in neurodegeneration?

A. Mitchell, F. Ali, Z. Xu, D. Fritz, S. Lewis, R. Carpenter et al. (UK)

Objective: To study saccadic eye movements in patients with Huntington's disease (HD) and Parkinson's disease (PD) versus age matched controls to evaluate their use as potential clinical biomarkers: their corre-

lation with presence or severity of disease, and the effect of symptomatic treatment.

Background: Eye movements are known to be affected in both PD and HD. We have chosen to measure saccadic latencies using newly developed equipment that allows for easy collection of a large data set. In the ideal world a biomarker would enable an accurate diagnosis of disease, would objectively track the progression of disease, and would be minimally, or at least predictably, affected by symptomatic treatment for the disease. We investigated these attributes for saccadic latency.

Methods: Ethical permission was granted to recruit patients and their relatives from the research clinics at the Cambridge Centre for Brain Repair. In total 23 patients with HD and 20 patients with PD were studied, together with 20 age-matched controls for each group. Furthermore, 15 patients with PD were studied on and off levodopa therapy. 300 saccades were recorded from each patient using the miniaturised infra-red saccadometer. The visual tracking task involved following a laser dot that was extinguished centrally as a similar dot appeared after a random delay either 10 degrees to its left or right.

Results: Each set of 300 saccadic latencies were plotted as a cumulative frequency histogram on reciprocal axes,¹ from which the median latency, slope and prevalence of early saccades could be determined. Saccade duration and its variability was also recorded. Patients with HD produced different saccades from the control group, such that in 2 test cases we were able to correctly predict genetic disease status on the basis of saccadic parameters. In addition we found a correlation between saccadic abnormalities and UHDRS score of disease severity. The results in PD were less clear cut, but we found that levodopa affects saccadic latency distribution.

Conclusion: Saccadic latency correlates to some extent with disease presence and severity, but may be affected by drug therapy. Further longitudinal work is required to determine the reproducibility of saccadic parameters and how saccadic distributions change over time.

Reference

1. Carpenter. *Nature* 1995;377,59–62.

P199

Gait disturbances in depressed patients: Effects of pharmacologic therapy

D. Paleacu, A. Shutzman, N. Giladi, T. Herman, J.M. Hausdorff (Israel)

Objective: To investigate the relationship between depression and gait and to evaluate the effects of anti-depressants (AD) on gait in depressed patients.

Background: Locomotion alterations are observable features of depressed patients, either due to disease itself or as an effect of medication. Depression is also a risk factor for falls in the elderly and this might also be related to medications. While the gait of depressed patients has been described, the effect of AD and their interrelationship has not been well studied.

Methods: 22 patients diagnosed with clinical depression, according to DSM-IV criteria, were recruited from a psychiatric outpatient clinic. The Hamilton Depression Scale (HAMD) was used to assess the affective status, the Mini Mental State Examination (MMSE) evaluated cognitive function and Barthel's Index of Instrumental Activities of Daily Living (IADL's) the functional independence. Patients walked for 2 min on level ground at their self-selected comfortable rate. Gait parameters were quantified using a stopwatch and force-sensitive insoles, where assessments were performed at baseline and after 10 weeks of AD treatment from the SSRI's or SNRI's group titrated to therapeutic doses.

Results: Patients mean age was 67.9 (SD12.9 years, 77% women). At baseline depressive symptoms, measured by the HAMD and MMSE scores were correlated (lower MMSE, worse, with higher HAMD $r = -0.66$, $P = 0.001$), but HAMD scores were not significantly correlated with any gait measure ($P > 0.10$). The therapy significantly improved the affective state; HAMD scores were reduced from 23.4 ± 6.3 at baseline to 9.7 ± 2.7 following treatment ($P < 0.001$). There were small but significant improvements in gait speed ($P = 0.033$) stride time variability ($P = 0.036$) and swing asymmetry ($P = 0.038$). Those with higher HAMD scores at baseline had more significant changes; $r = -0.80$; $P < 0.001$), but HAMD changes were not associated with gait changes.

Conclusions: Although AD have been previously blamed for increasing fall risk, the present findings demonstrate that therapy with AD from the SSRI or SNRI group improves gait steadiness and reduces markers of fall risk. Nonetheless, the lack of an association between changes in depression and changes in gait suggests that other factors likely mediate this interdependence.

P200

Ancient descriptions of movement disorders. Cathedral El Burgo de Osma (Soria, Spain)

P.J. Garcia Ruiz, J.J. Ruiz, A. Garcia Torres, S. Fanjul (Madrid, Spain; Zamora, Spain; Madrid, Spain)

Objective: To show some ancient descriptions of movement disorders at the Cathedral El Burgo de Osma (Soria, Spain)

Background: The cathedral of Burgo de Osma (Soria) is one of the finest examples of monumental architecture in Spain. It was built over a long period of time (XII–XVIII) and several styles (including gothic style) were used in its construction.

Results: Inside the cathedral, it is possible to find several sculptural examples of movement disorders including two cases with cervical dystonia (a peasant with 90° cervical tilt to the left). In addition, there is a vivid description of a priest with stooped posture, half open mouth, staring expression, and a very notorious anterocollis. The author depicted a man with parkinsonism, probably atypical parkinsonism.

Conclusion: It is possible to find in ancient arts, vivid descriptions of movement disorders. Several other examples are discussed.

P201

A clinical follow-up study of the natural history and daytime somnolence in 94 patients with restless legs syndrome (RLS) attending a specialist clinic in the UK

S. Tluk, J. Bland, P. Patel, K.R. Chaudhuri (London, UK)

Objective: To record the natural history of RLS, its periodicity, effect on daytime somnolence and response to relevant treatment in a group of RLS patients attending regional tertiary/secondary care based clinics.

Background: Aspects of the natural history of RLS in relation to response to treatment, progression of symptoms, and effects such as daytime somnolence remain unclear and little data is available from the UK.

Methods: This is a retrospective audit based study supplemented by prospective clinical follow up. The ethnicity, clinical and biochemical profiles of 94 consecutive RLS patients referred to movement disorders clinic in an inner London area using a standard structured questionnaire over a mean 2-year (range 0.5–6 years) follow-up period were recorded and reviewed. 25 complained of sleepiness and completed the Epworth sleepiness scale (ESS).

Results: Overall, 94 patients [mean age 55.4 years (28–85), 66% females, mean duration of RLS 7.8 years (0.6–41 years)] have been followed up over a mean period of 2 years (1998–2004). 17% had Parkinson's disease while another 11.4% referred had multiple sclerosis (MS) in addition to RLS. Paroxysmal pain was a dominant feature in 21.2% while 4.2% had paroxysmal RLS. Periodic limb movements (PLM) was present in 19.1% and 8.5% also reported "restless hands" in association with RLS. In idiopathic RLS without PD ($n = 77$), 24 were on dopamine agonists (cabergoline mean dose 1.9 mg, ropinirole 0.3 mg, pramipexole 1.2 mg) and 2 on levodopa. Longest follow-up period on agonists was 5 years. Augmentation was seen in 6.3% (on cabergoline and pramipexole). Mean ESS score was 11.2 (4–20) and mean ferritin levels was 73.3 mcg/dL (4–606). Work-related accidents due to drowsiness was reported in 4 with high ESS scores.

Conclusions: Our clinical follow-up study indicates that RLS may be associated with daytime drowsiness and in such patients ESS is an useful assessment tool. Pain and involvement of hands may occur in IRLS even without augmentation and dopamine agonists continue to be useful in RLS even in the long term.

P202**PLM counting in PSG: Role of the amplitude**

V. Gschliesser, E. Brandauer, H. Ulmer, B. Hög, W. Poewe (Innsbruck, Austria)

Objective: We investigated the relationship between periodic limb movement (PLM) counts obtained with standard scoring criteria and PLM counts scored according to the same criteria except the amplitude criterion in a mixed sleep disorder population.

Background: Periodic limb movements (PLM) during sleep are recorded and scored according to standard criteria. Scoring criteria indicate that tibialis anterior muscle activation in EMG with a burst duration between 0.5 to 5 s, an amplitude over 25% of calibration movements and with an interval of at least 5 s and no more than 90 s between their onsets, occurring in series of 4 or more LM are counted for PLM.

Design/Methods: 24 patients (mean age 57.5 ± 12.0 years) with a PLM index (PLMI) >5 per hour in a previous polysomnography (PSG) underwent a full night (8 h) of digital PSG. PLM were recorded and manually scored according to standard criteria manually for time in bed (TIB), NonREM, REM sleep and wakefulness. PLM in wakefulness were scored with a maximum duration of 10 s. In a second step we counted PLMS without the amplitude criterion for the same subjects and the same nights and compared the PLM counts obtained with both methods.

Results: The PLMI was 34.4 ± 30.7 PLM/hour (h) and 50.2 ± 36.4 PLM/h with/without amplitude criterion (AC) for TIB. This difference was statistically significant ($P < 0.001$, Wilcoxon test). The PLMI with/without AC in NonREM sleep was 27.5 ± 24.3 and 38.5 ± 28.4 ($P < 0.001$, Wilcoxon test), in REM sleep 1.5 ± 2.7 and 3.7 ± 5.0 ($P = 0.001$, Wilcoxon test) and in wakefulness: 5.4 ± 9.6 and 7.9 ± 11.7 ($P < 0.001$, Wilcoxon test).

Conclusions: PLM counts are significantly lower when the amplitude criterion is used than when it is omitted. This may relate to the fact that counting without AC increases the sensitivity to detect single leg movement, and allows for identification of PLM sequences which would not have fulfilled the periodicity criteria otherwise. The strict application of the amplitude criterion is difficult as instructions are mainly qualitative. Moreover, the amplitude criterion is an arbitrary variable and its clinical significance is uncertain. Further studies should determine, if PLM counts without AC are more useful to detect the activity of the periodic oscillator underlying PLM.

P203**Characteristics and antidepressant treatment outcomes of patients with psychogenic movement disorder: A naturalistic study**

V. Voon, A.E. Lang (Toronto, Ontario, Canada)

Objective: To describe the psychiatric assessment and antidepressant treatment outcomes of psychogenic movement disorder (PMD).

Background: PMD is a subtype of conversion disorder (CD); chronic CD has a poor prognosis.

Methods: Twenty-three consecutively referred chronic PMD outpatients underwent psychiatric assessment. Fifteen agreed to antidepressant treatment and were followed in a naturalistic manner. Concurrently, three had supportive psychotherapy and one had family intervention. Patients were assessed with the DSM IV-based Mini International Neuropsychiatric Inventory; depression, anxiety, motor, and global severity were assessed.

Results: 18 (78%) had at least one Axis I diagnosis; 9 (39%) 2 or more. 3 (13%) had somatization disorder; 12 (52%) stressors at onset; and 2 (9%) abuse history. 5 (22%) had previous psychiatric contact. 9 (39%) had previous antidepressants but only 4 (17%) had adequate trials. No significant differences existed between treated and untreated groups. In the treated group, mean age was 50.2 years (SD 15.7) and illness duration 56.3 months (SD 50.8). The Montgomery Asberg Depression Rating Scale scores improved from baseline following antidepressants ($P < 0.01$). Two treated subgroups were identified: 10 (66%) had primary conversion symptoms of which 8 had marked motor and global improvements with 7 attaining remission; 5 (33%) had primary hypochondriasis, somatization disorder, or probable factitious/malingering of which none improved. All

of the former subgroup had a current or previous depression or anxiety compared to 40% in the latter. Three of the improved patients did not have current depression or anxiety but had recent depression.

Discussion: Chronic PMD with primary conversion symptoms may respond to antidepressants in keeping with reports of antidepressant efficacy in functional somatic syndromes. The prognosis may depend on the identification of other primary disorders. Depression or anxiety along with its syndromal forms may play a role in mediating the PMD symptom. There may also be a direct role of the antidepressant, suggesting a potential serotonergic mechanism in PMD symptoms. The limited previous psychiatric contact given the symptom chronicity emphasizes the necessary role of appropriate diagnosis and referrals for treatment.

P204**Ropinirole is an effective, well-tolerated treatment for moderate-to-severe RLS: Results of a US study**

R. Bogan, M.G. Connolly, G. Rederich (Columbia, USA; Alabaster, USA; Redondo Beach, USA)

Objective: To assess the efficacy and safety of ropinirole in the treatment of patients with RLS.

Background: RLS (Ekbom syndrome) is a neurological disorder affecting 5–10% of the population at any frequency/severity. Patients experience an irresistible urge to move and distressing sensations in the legs, that occur/worsen during the night or at rest, and that may severely disturb sleep. RLS has been linked to dopaminergic dysfunction and dopamine agonists have been recommended as first-line therapy for moderate-to-severe RLS.

Methods: TREAT RLS US (protocol 101468/249) was a double-blind, phase-III study conducted in 47 US centers. Patients diagnosed with moderate-to-severe idiopathic RLS were randomized (1:1) to ropinirole or placebo for 12 weeks. Ropinirole was titrated from 0.25 mg/day to a maximum of 4.0 mg/day, once daily 1–3 h before bedtime, subject to an optimal balance of efficacy and tolerability.

Results: Of the 380 patients randomized, 187 received ropinirole and 193 placebo. After 12 weeks, the mean dose of ropinirole was 2.15 ± 1.18 mg/day and 37/187 (19.8%) patients were receiving 4.0 mg/day. Mean improvement in International Restless Legs Scale score at week 12 last observation carried forward (LOCF), was significantly greater with ropinirole than placebo (adjusted mean treatment difference: -3.7 ; 95% CI: $-5.4, -2.0$; $P < 0.0001$). A significantly higher proportion of patients receiving ropinirole had a score of much improved or very much improved on the Clinical Global Impression-Improvement scale (137/187; 73.3%) compared with placebo (109/193; 56.5%; adjusted odds ratio: 2.1; 95% CI: 1.4, 3.3; $p = 0.0006$) at week 12 LOCF. The three most common adverse events (AEs) in ropinirole-treated patients were nausea, headache, and somnolence. The rate of withdrawal due to AEs was similar between the groups (ropinirole: 7/187, 3.7%; placebo: 9/193, 4.7%).

Conclusions: These data show that ropinirole significantly and effectively relieves the symptoms of moderate-to-severe RLS and is generally well tolerated in patients from the US.

P205**Walking is more like catching than tapping: Gait in the elderly as a complex cognitive task**

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Objective: To test the hypothesis that walking among older adults has more in common with a motor planning task like catching an object than it does with an automated task like repetitive, rhythmic tapping.

Background: In the past, walking has generally been viewed as an automated, rhythmic motor task. However, recent studies using dual task paradigms have demonstrated that gait depends on attention and higher-level cognitive input, at least when a second task takes place in parallel to walking.

Methods: 43 community-living older adults (mean: 71.9 years) who could walk independently were studied. Subjects were free from overt gait

and cognitive disturbances, neurological, affective, orthopedic or other co-morbidities likely to impact gait. We quantified their gait, tapping, catching skills, and cognitive function. Gait speed and the average value and the co-efficient of variation (CV) of the stride time were determined during a 2-min walk. The CV assesses the stride-to-stride variability, a measure previously associated with fall risk. A computerized cognitive assessment battery (Mindstreams®; NeuroTrax Corp.) evaluated tapping, catching, and cognitive function. The average inter-tap interval and tapping variability were quantified. Catch-game measures included time to first move, number of direction changes of the paddle, accuracy, and degree of errors.

Results: Tapping measures were not significantly associated with any gait parameter ($P > 0.07$). In contrast, catch-game performance was significantly associated with stride time variability ($r = 0.43$, $P < 0.006$) and gait speed. Memory was not associated with any measure of gait ($P > 0.11$). Stroop test measures were not associated with gait speed, but were correlated with stride variability ($r = -0.42$, $P < 0.009$). When subjects were stratified based on their performance on the Stroop test and tests of memory, stride time variability was highly dependent on the former ($P < 0.006$), but not the latter ($P = 0.975$).

Conclusions: Among older adults, routine walking relies upon executive function and has more in common with complex motor tasks, like catching, than it does with tapping. These findings underscore the interconnectedness of gait and higher-level cognitive function, and suggest an alternative approach to the treatment of fall risk in the elderly.

P206

Predictors of health-related quality of life (HRQL) in US respondents suffering from RLS

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(Manchester, UK; Baltimore, Maryland, USA; Greenford, UK)

Objective: The objective of this study was to establish the key aspects of RLS most closely associated with detrimental impacts on HRQL. Statistical relationships between various measures of RLS and HRQL for a sample of respondents with RLS were assessed.

Background: RLS (Ekbom syndrome) is a common, underdiagnosed, neurological sensorimotor disorder, characterized by an overwhelming urge to move the legs, and often associated with unpleasant sensations in the legs. This condition is known to have a significant impact on sufferers' HRQL. However, little is known about the determinants of HRQL in respondents with RLS.

Methods: Short Form (SF)-36 data was collected as part of an omnibus survey of respondents who screened positive for RLS in the USA. Other variables collected included demographics, self-reported severity of symptoms, degree of distress, and medical care. Relationships between these variables and the eight domains of the SF 36, the overall physical (PCS) and mental (MCS) summary component scores, were explored with multiple regression analysis using Ordinary Least Squares.

Results: Of the 6014 people surveyed, 454 (7.5%) screened positive for RLS and 424 of these completed the SF-36 (mean age for those completing the SF-36, 53 years; SD 16).

Respondents reporting severe RLS symptoms had significantly lower HRQL across all SF-36 domains than those reporting mild symptoms.

Patients reporting moderate or extreme distress about their RLS symptoms had significantly inferior HRQL on the Social Functioning domain than those reporting little or no distress ($p = 0.018$).

Significantly diminished HRQL across a number of SF-36 domains was seen in respondents currently treated with prescription medication compared with those not treated.

The number of GP and specialist visits reported showed predictive capability across a number of physical domains.

Conclusions: This is the first study to investigate the determinants of HRQL in patients with RLS. Diminished HRQL in this sample was partly accounted for by the severity and distress from symptoms. The association of treatment and frequency of physician visits with lower HRQL may reflect increased use of healthcare resources by those most affected by RLS.

P207

Establishing the relationship between RLS severity and work productivity impairment associated with RLS

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Objective: To assess the relationship between RLS severity as measured using the International Restless Legs Scale (IRLS) and work productivity impairment associated with RLS symptoms.

Background: RLS (Ekbom syndrome) is a common, underdiagnosed neurological movement disorder, which is characterized by an overwhelming urge to move the legs due to unpleasant sensations. This condition is known to have a significant impact on sufferers' health-related quality of life. However, little is known about the relationship between RLS severity and the indirect costs on an individual's daily activities and productivity.

Methods: The baseline data from two pivotal, phase-III clinical trials (TREAT RLS 1 and 2) were combined for all employed patients completing both the IRLS, a measure of RLS severity; and the Work Productivity and Activity Impairment (WPAI) questionnaire, a measure of work productivity. Linear regression analysis of individual patient data from the IRLS and WPAI was performed using SPSS. The dependent variable was percent overall work impairment due to RLS at baseline, and the independent variable was the baseline IRLS severity. The regression analysis included controls for sex, centre, age, and treatment to identify differences within these groups. ANOVA and "difference in means" was used to establish the statistical significance of the results.

Results: The combined sample population included 272 participants who had completed both questionnaires at baseline. The regression analysis indicated a statistically significant causal relationship between the dependent and independent variables ($P < 0.0001$). The regression model predicts that a 1.728 unit increase in the IRLS severity results in approximately a 1% increase in activity and work impairment. All control variables were found to be statistically insignificant, which was consistent with our null hypothesis of no difference between groups at baseline.

Conclusions: The results indicate that patients with more severe RLS are likely to suffer from greater work productivity impairment. The relationship between RLS severity based on IRLS scores and productivity can be used to establish indirect costs of RLS.

P208

A study of occurrence of restless legs syndrome (RLS) and transferrin receptor assay in an anaemic and non-anaemic multi-ethnic population attending a haematology clinic in inner city, London, UK

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Objectives: To assess the frequency and prevalence of RLS using (a) the standard diagnostic criteria in white and black populations with or without anaemia attending a haematology clinic, and (b): to address the usefulness of measuring transferrin receptor (TR) in the diagnosis of RLS.

Background: Studies have established that RLS is common in iron deficient subjects while its occurrence in an unselected group of anaemic patients, particularly in a multi-ethnic population including African-Caribbean (AC) patients is unclear. Also although, ferritin levels (ref. Range = 15–200 $\mu\text{g/L}$) are used to monitor RLS, TR assay (ref. range = 0.76–1.76 mg/L) may be a more reliable marker.

Methods: Standard questionnaire was administered to consecutive patients attending haematology clinics for anaemia and other haematological disorders over a 3-month period. Blood was collected for ferritin and TR assay after informed consent.

Results: Overall 125 questionnaires (mean age 59 years, Male(M): Female(F) 1:1.7) were collected, 68 with anaemia (55.4%) from various causes. 59.2% were White Caucasian (mean age 66.7 years, M:F 1:1.9) while 28% were Black (AC, mean age 45 years, M:F 1.2:2). Overall RLS rate was 22.4% while in anaemic subjects the rate was 25% and non-anaemic 19.3%. In the White subjects, 22.9% had RLS while in the AC group RLS rate was 22.7%. Painful RLS was present in 43% of all cases while severe RLS was present in 46%. Ferritin levels were 132.56 $\mu\text{g/L}$

(including transfused patients) and TR level was 4.6 mg/L in anaemic while in non-anaemic ferritin level was 58.4 µg/L and TR 2.4 mg/L.

Conclusions: (1) Our study shows a striking increase in the occurrence of RLS in anaemic and non-anaemic subjects compared to prevalence figures in general population (7% locally), (2) There is a high RLS frequency in black AC patients (22.7%), an ethnic group in whom RLS prevalence figures are unknown, and (3) TR assays may be a more reliable indicator of iron status compared to ferritin level in anaemic population.

P209

Screening for cognitive deficits in Parkinson's disease—Which marker relates to disease severity?

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Objective: To search for markers of cognitive impairment related to disease severity in subjects with Parkinson's disease.

Background: Cognitive deficits are important symptoms of central nervous system diseases and the prevalence increases with age. At present, the frequency and pattern of cognitive deficits in subjects with Parkinson's disease and the distinction from other causes of progressive cognitive impairment such as Alzheimer's disease is under discussion.

Methods: In an ongoing study we assessed until now 106 consecutive subjects with Parkinson's disease (66.4 ± 8.9 years (mean ± standard deviation); average duration of disease 3.5 ± 1.3 years) diagnosed in outpatient or inpatient service specialized for the diagnosis of Parkinson's disease.

Results: The number of patients with Hoehn and Yahr stage 1 to 4 were 13, 45, 36, and 12, respectively. As screening instruments we used established cognitive screening instruments for the assessment of memory (Buschke Memory Impairment Screen), attention (Letter Sorting Test), and a verbal fluency task (semantic fluency). About one half of the subjects in Hoehn and Yahr stages 1 to 4 had deficits in the memory task. In contrast, performance in the Letter Sorting Test and the fluency task declined with increasing Hoehn and Yahr stage.

Conclusions: First, the present results show that cognitive deficits are frequent in subjects with Parkinson's disease. Second, even with simple screening instruments cognitive deficits related to severity of Parkinson's disease may be distinguished from frequent cognitive deficits unrelated to disease severity.

P210

Tolerability of a forced-dose escalating regimen of ropinirole in patients with RLS

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Objective: To assess the tolerability of ropinirole in patients with RLS using a forced-titration approach.

Background: RLS (Ekbom syndrome) is a neurological disorder characterized by sensory and motor symptoms that can affect sleep. In an extensive program of trials, ropinirole, a dopamine agonist, has demonstrated efficacy in the treatment of RLS over a dose range of 0.25–4.0 mg/day.

Methods: This double-blind, parallel-group trial (protocol 101468/207) randomized patients with RLS in a 2:1 ratio to ropinirole (n = 37) or placebo (n = 17), given once daily, 1–3 h before bedtime. Treatment dose was force-titrated from 0.25 mg to 4.0 mg over 7 weeks, with the maximum dose dependent on tolerability. Adverse event (AE) and vital sign data were obtained at each dose level to define the maximum tolerated dose (MTD).

Results: Of the 37 ropinirole-treated patients, 29 (78.4%) completed the study, and 16 (43.2%) tolerated the highest dose (4.0 mg). At least 70% of patients exposed tolerated each dose level of ropinirole. A MTD was defined for 34/37 patients receiving ropinirole (91.9%); the median MTD was 2.75 mg. A total of 35 patients receiving ropinirole (94.6%) experienced 237 AEs and 13 patients receiving placebo (76.5%) experienced 39 AEs during treatment. The majority of AEs reported in the ropinirole group were mild or moderate in intensity (224/237; 94.5%), with no unexpected or serious AEs. The most frequently reported AEs in the ropinirole group

were nausea (22/37; 59.5%), headache (43.2%), dizziness (29.7%) and somnolence (29.7%), and vomiting (18.9%). Most of these occurred on the first day of a new dose level (50.0–74.2%) and lasted for less than 1 day (75.0–100.0%). There were no AEs of syncope, sudden onset of sleep, hallucination, or augmentation. In addition, the mean (2SE) change in International Restless Legs Scale (IRLS) total score from baseline to final dose for the ropinirole group (n = 29) was –15.6 (±3.27) compared with –6.1 (±3.77) for placebo (n = 13).

Conclusions: The pattern of AEs was typical of a dopamine agonist and the frequency reflected the force-titration study design. The high percentage of patients tolerating each dose level of ropinirole and the improvement in IRLS score suggests that this dosing regimen is generally well tolerated and effective in patients with RLS.

P211

Incidence of dyskinesias in a 10-year naturalistic follow-up of patients with early Parkinson's disease (PD) initially receiving ropinirole compared with L-dopa

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Objective: To assess, in an open naturalistic study (showing normal clinical practice), the long-term progression of PD, and treatment effects in patients initially randomized to ropinirole or L-dopa.

Background: The 5-year 056 study¹ showed that patients initially receiving ropinirole develop fewer dyskinesias than those initially receiving L-dopa. To assess longer-term benefits of ropinirole, patients completing study 056 could enter a 5-year follow-up extension protocol.

Methods: Patients could receive any treatment during follow-up, unrestricted by the original randomization. Treatment efficacy and incidence of dyskinesias were assessed every 6 months with the Unified PD Rating Scale (UPDRS). Total follow-up was 10 years. Results are reported for patients in their original randomization groups (regardless of current therapy).

Results: Of the 268 patients initially randomized in study 056, 130 completed the trial and 69 entered this study (42, ropinirole; 27, L-dopa). The main demographic variables of this subgroup were comparable to those in the initial study. At 10 years, the incidence of dyskinesias in the ropinirole group (52.4%) remained significantly lower than in the L-dopa group (77.8%), adjusted odds ratio = 0.3, 95% CI 0.1–1.0, *P* = 0.0457. Median time to develop dyskinesias was significantly longer in the ropinirole group (8.6 vs. 7.0 years; adjusted hazard ratio = 0.4, 95% CI 0.2–0.8, *P* = 0.0065). Both groups showed a small worsening from baseline in motor and ADL scores, with no significant treatment differences.

Conclusions: In this 10-year follow-up, naturalistic study, patients who received initial treatment with ropinirole maintained a significantly lower risk of dyskinesias 10 years after the start of therapy. At the same time, these patients had good treatment efficacy, similar UPDRS motor and ADL scores to those who started treatment with L-dopa. The fact that only 25% of the initial randomized population could be followed-up for 10 years reduces the strength of the present findings but still supports the initial use of ropinirole as part of a long-term strategy for the management of PD.

Reference

1. Rascol O. *N Engl J Med* 2000;342:1484–1491.

P212

A segregation analysis of the restless legs syndrome (RLS) using age-of-onset models

W.A. Hening, R.A. Mathias, R.P. Allen, M. Washburn, S. Lesage, C.J. Earley, et al. (New York City, New York, USA; Baltimore, Maryland, USA)

Objective: To determine the inheritance pattern of RLS in a segregation analysis of families of RLS patients.

Background: Familial aggregation has long been suspected in RLS, but has received little formal investigation. A segregation analysis done in Germany found a successful fit for a major gene model with dominant

inheritance, but only in families having an average age of onset below 30¹. 3 candidate loci have been reported on different chromosomes in distinct populations using different techniques and models.

Methods: Probands were consecutive RLS patients presenting to the Neurology and Sleep clinics at Johns-Hopkins Bayview who were willing to have first- and second-degree relatives contacted. An RLS diagnosis was made in those who endorsed the four diagnostic features of RLS and whose symptoms could not be explained by an alternate diagnosis. Those with uncertain diagnoses were excluded from analysis. 77 pedigrees were analyzed with 590 phenotyped subjects including 281 diagnosed with RLS. A commingling analysis was done to determine if there was more than one distribution of ages-of-onset in subjects with RLS. The patterns of inheritance of RLS were examined using age-of-onset models in segregation analyses carried out using the REGTL subroutine in SAGE 3.1.

Results: The commingling analysis found two distributions of ages-of-onset; ages-of-onset below 26.35 were more likely to fall into an early distribution. Initial results of the age-of-onset models suggest that neither purely environmental nor major gene models fit the pedigrees.

Discussion: Our results are consistent with an important genetic contribution to development of RLS, but suggest that the underlying genetic model may be polygenic. Consistent with the three loci previously reported for this disorder, it is likely that multiple susceptibility alleles will be found whose importance may vary in different populations.

Reference

1. Winkelmann et al., 2002.

P213

Continuous intrathecal morphine application in therapy refractory restless legs syndrome (RLS)

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Objective: Some RLS patients get refractory to any kind of therapy (L-dopa, dopaminagonists (DA), antiepileptic drugs, benzodiazepines and central acting analgesics) or the dosage needed leads to intolerable side effects.

Background: During the last meeting of the *Movement Disorder Society* we reported the 2 first cases of patients being treated by continuous intrathecal morphine application (Mov Disord 2004;19(Suppl. 9):S416–S417). We now present our third (female) patient. The diagnosis of familiar RLS was settled up at the age of 37 according to the criteria of the International Restless Legs Study Group and confirmed by polysomnography (PSG). Symptomatic forms were excluded by clinical examination, neuro-electrophysiology and laboratory analysis. She rapidly developed augmentation and symptom shift to L-dopa and DA and got refractory to the other kinds of treatments or developed side effects. As a result of the urge to move all of the time and the chronic sleep deprivation she developed a severe depression.

Methods: At the age of 41 the patient gave her consent to intrathecal morphine applied by consecutive lumbar puncture (initial dosage 0.05 mg morphine). At the dosage of 0.1 mg a satisfactory complaint relief was achieved without any side effects, the result was confirmed by PSG. Consecutively an intrathecal catheter was implanted and connected, in a second operative step, to an electronic pump device (Medtronic) located between the skin and the abdominal muscle layers (September 2004). The initial dosage of morphine was 0.2 mg/24 h, the dosage was increased to 0.3 mg/24 h in November 2004.

The follow-up of our previously reported patients has extended to 19 months (patient 1, 41 years of age) respectively 12 months (patient 2, 76 years of age). Both are on the same dosage as reported before (0.25 mg/24 h and 0.3509 mg/24 h). In patient 1 an "emergency" medication of 150 mg of tramadol has been prescribed meanwhile for use during stressing days. None of the 3 patients has reported side effects until now. The further follow-up will be reported at the meeting.

Conclusion: Continuous intrathecal morphine application is helpful in therapy refractory RLS patients. Until now the treatment is well tolerated.

P214

Four case reports of multiple confusional arousals in a single night mistaken for nocturnal seizures

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Objective: To report occurrence of multiple episodes of confusional arousals in a single night in four patients which have been mistaken for nocturnal seizures.

Background: Confusional arousal (CA) is a partial arousal disorder, which generally occurs during slow wave sleep as a single episode. Multiple episodes of CA in a single night are extremely rare and may be mistaken for nocturnal seizures.

Design/Methods: Four patients (Pt 1, an 11-year-old boy; Pt 2, a 13-year-old brother of pt 1; Pt 3, a 6-year-old boy; Pt 4, a 4-year-old girl) presented with history of multiple episodes of nocturnal spells. During the spells the subjects would sit up in bed, look confused and unresponsive without fearful appearance, and after several minutes would go back to sleep. On some occasions when the mother forced patient 1 to lie down, he started struggling and sleep walking. None of them had clonic movement, tongue biting or urinary incontinence. These spells occurred both in the early and late part of the night.

Results: Video polysomnography study including 16 channel EEG recording showed 3–4 episodes of arousals with behavioral confusion but without choreoathetoid, ballismic or clonic movements, epileptiform discharges or sleep apnea. Patient 3 was treated by several neurologists with anticonvulsants without benefit for a mistaken diagnosis of nocturnal seizure and in patient 4 a diagnosis of partial complex seizure was strongly considered.

Conclusions: It is important to be aware of these unusual manifestations of CA from which the youngster will generally outgrow. The clues are the occurrence of EEG arousals usually from slow wave sleep without epileptiform discharges and the behavioral confusion without abnormal movements or response to anticonvulsants. A correct diagnosis will eliminate unnecessary costs and adverse effects of anticonvulsants.

P215

A polymyographic and polysomnographic analysis of painful and painless legs moving toes syndrome

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Objective: To report polymyographic analysis during overnight polysomnography (PSG) in two patients with painful and painless legs moving toes syndrome (PPLMTS).

Background: Since its original description in 1971, both painful and painless legs as unilateral or bilateral presentations have been described in scattered reports attesting to the heterogeneity of this entity. Pathophysiology of PPLMTS remains uncertain. Most cases result from a peripheral cause but some are caused by CNS lesion. Very limited electrophysiologic analysis showed two distinct EMG burst patterns, although PSG study has rarely been performed.

Design/Methods: Patient 1 is a 53-year-old woman with a 6-year history of involuntary continuous or semicontinuous flexion-extension movements of the right toes associated with disagreeable pain. She also has lower back pain radiating to the right foot. Patient 2 is an 81-year-old woman with Parkinson's disease for 1 year on sinemet who developed painless flexion-extension, abduction-adduction movements of toes bilaterally. She also has symptoms consistent with mild restless legs syndrome.

Results: Overnight PSG including polymyography in patient 1 showed short and long synchronous dystonic bursts in the right extensor digitorum brevis (EDB) and flexor hallucis brevis (FHB) muscles predominantly during wakefulness but also during stage 1 NREM and REM sleep and stage transitions along with nonspecific sleep architectural changes. Similar recording in patient 2 showed a mixture of myoclonic and dystonic EMG bursts which are synchronus, asynchronus, or alternating, mostly during wakefulness and stage transitions but occasionally during REM sleep and

stage 2 NREM sleep. EMG and MRI findings of patient 1 suggested lumbar disc disease and radiculopathy.

Conclusions: PPLMTS is a heterogenous syndrome both clinically and electrophysiologically. A mixture of dystonic, myoclonic, synchronous, asynchronous and triphasic EMG bursts suggests complex pathophysiology and CNS command to spinal interneurons and ventral horn cells which may be determined by both peripheral afferent and supraspinal efferent control.

P216

Recurrent facial palsy with contralateral hemifacial spasm (19 attacks). An association with HSV1?

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Objective: To report an unusual case of recurrent *unilateral* facial palsy with simultaneous *contralateral* hemifacial spasm.

Background: This type of synkinesis has been rarely documented. We highlight important clinical, diagnostic and therapeutic issues.

Methods: A 44-year-old woman had her 1st attack of left facial palsy in 1988 after a flu-like illness. She recovered in 3 months. A milder 2nd attack was in 2002. Later in 2002, the 3rd attack of left facial palsy started more abruptly over minutes. There was associated headache, left cheek and upper lip numbness. Simultaneously, she noted a constant right facial "pulling." She was treated with oral steroids and aciclovir and recovered fully. Over the next 24 months, she had 16 almost identical attacks, each with a left LMN facial palsy and most with a right tonic hemifacial spasm (Video 1). This combination caused a profound facial distortion and interfered with speech and work. Each attack would last 2-4 weeks and would resolve, sometimes partially and sometimes abruptly. Hearing, taste and salivation were normal. Four family members suffered Bell's palsy and one suffered trigeminal neuralgia. Two cousins had multiple sclerosis.

Results: On 3 occasions she was investigated during an attack (Table 1). Extensive investigations with imaging, EEG, blood tests, CSF analysis and lip biopsy were unrevealing but on 1 occasion HSV1 DNA was isolated from her CSF by PCR amplification (double + ve). Contrary to previous reports, her blink responses were repeatedly normal. She has suffered from 4 discrete episodes of chicken pox, 2 of shingles and is undergoing assessment of her T cell immune responses. Prior to the HSV1 result, each attack was treated with oral prednisolone and high dose oral aciclovir. A response to the steroids was not clear. She was allergic to valaciclovir and famciclovir. Prophylactic medium dose oral aciclovir reduced the frequency of attacks from 12/year to 4 in 9 months. Carbamazepine was ineffective. We elected not to offer botulinum toxin or iv immunoglobulin as the frequency of attacks is declining.

Conclusion: Unilateral facial palsy with simultaneous contralateral hemifacial spasm is an unusual movement disorder of unclear pathophysiology. This type of synkinesis can be disabling and difficult to treat.

P217

Blood pressure variation as a component of autonomic arousal in association with periodic limb movements in sleep in patients with restless legs syndrome

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Objective: To determine changes in blood pressure associated with periodic limb movements in sleep (PLMS) in patients with restless legs syndrome (RLS).

Background: Blood pressure monitoring in 1 patient with PLMS was documented more than 10 years ago which showed a rise associated with the PLMS. Various studies have demonstrated a change in pulse rate with PLMS. This study is done to verify that blood pressure does rise with PLMS and to correlate changes in blood pressure with changes in pulse rate at the time of PLMS.

Design/Methods: Three female patients ages 30, 60, and 66 years with RLS and PLMS were asked to lie in bed prior to polysomnography and imitate PLMS which were recorded with EMG. The patients were asked to flex the right foot alternating with the left foot every 10 s for 5 min. Any involuntary PLM during wakefulness were also recorded as were PLMS during sleep. Blood pressure and pulse rate were continuously monitored under all three of these conditions. Changes in blood pressure and pulse rate at the time of PLM were compared under these three conditions.

Results: For the 3 patients 75 involuntary PLMS during sleep and 75 voluntary PLM in wakefulness were analyzed. There was a rise in blood pressure noted after the voluntary imitated PLM of 0-2 mmHg which persisted for 2-3 s after the movements. There was a rise in blood pressure noted after the involuntary PLMS in sleep that was higher and more persistent (7-12 mmHg for 7-9 s). A preliminary examination of the involuntary PLM in wakefulness also suggest a rise that was much higher than noted with the voluntary PLM in wakefulness. We also noted that for all 3 conditions the pulse rate also increased with a magnitude proportional to that seen with the rises in blood pressure.

Conclusions: There was a rise in blood pressure and pulse rate noted during involuntary PLM in sleep and wakefulness which far exceeded that seen with voluntary mimicked PLM in wakefulness. The rise in the blood pressure and pulse rate can be a component of autonomic arousal seen with PLMS. Since most patients with RLS have PLMS, the rise of blood pressure in patients with PLMS may be an indicator of the previously noted association of hypertension and heart disease with RLS.

P218

The effective dose of Ropinirole in the treatment of patients with RLS

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Objective: To investigate the effective dose range of ropinirole in the treatment of RLS.

Background: RLS (Ekbom syndrome) is a chronic neurological disorder, associated with sleep disturbance and impaired quality of life (QoL). The

TABLE 1. Abstract 218

	RESET PLM	TREAT RLS1	TREAT RLS2	TREAT RLS US
All patients				
N	32	146	131	187
Mean (SD)	1.8 (1.01)	1.9 (1.13)	1.9 (1.19)	2.2 (1.18)
Median (range)	1.5 (0.5-4.0)	1.5 (0.25-4.0)	1.5 (0.25-4.0)	2.0 (0.25-4.0)
Improved patients*				
N	17	78	78	137
Mean (SD)	1.6 (0.85)	1.7 (1.04)	1.5 (0.95)	2.1 (1.18)
Median (range)	1.5 (0.5-3.0)	1.5 (0.25-4.0)	1.5 (0.25-4.0)	2.0 (0.25-4.0)

*Patients with a score of "very much improved" or "improved" on the CGI-I scale SD, standard deviation.

efficacy and tolerability of the dopamine agonist ropinirole in the treatment of RLS have been assessed in a comprehensive clinical trial program.

Methods: The four 12-week, randomised (1:1), double-blind, placebo-controlled studies: TREAT RLS 1, TREAT RLS 2, RESET PLM, and TREAT RLS US (protocol numbers: 101468/190; 101468/194; 101468/191; 101468/249) involved adults with moderate-to-severe idiopathic RLS. Once-daily treatment dose, taken 1–3 hs before bedtime, was titrated from 0.25 mg/day to a maximum of 4.0 mg/day, according to efficacy and tolerability. Treatment effects were measured using the proportion of patients with Clinical Global Impression-Improvement (CGI-I) score of very much improved or improved at week 12 last observation carried forward (LOCF).

Results: The mean and median doses (mg/day) of ropinirole at week 12 LOCF in all patients and at response on the CGI-I scale are shown in a table.

Conclusions: Data from this RLS clinical trial program show that ropinirole is effective at doses ranging from 0.25 to 4.0 mg/day. Although some patients have an initial response at the 0.25 mg/day dose, most patients titrated to and responded at doses of up to 2.0 mg/day. In a small proportion of patients, it was necessary to titrate up to 4.0 mg/day to achieve a response.

P219

Severity of restless legs syndrome in the general community

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Background: The prevalence of restless legs syndrome (RLS) has been reported to be around 10%. The distribution of disease severity in the general community is unknown.

The aim of the study was to assess the prevalence and severity of RLS in the general community.

Methods: Cross sectional study of a sex- and age-stratified random sample of the general population of Bruneck, South Tyrol (Northern Italy). A total of 701 subjects, aged between 50 and 89 years, participated in this survey. The diagnosis of RLS was established by face-to-face interviews according to standard criteria, severity was graded on severity scale of the International RLS study group (IRLS).

Results: The prevalence of RLS was 10.6% (14.2% in women, and 6.6% in men). According to the IRLS, 33.8% of all RLS patients had mild (IRLS 1–10), 44.6% moderate (IRLS 11–20), and 21.6% severe disease (IRLS 21–30). None of the subjects with RLS belonged to the category of very severe RLS (IRLS 31–40). None had been previously been diagnosed or was on dopaminergic therapy.

Discussion: Results of this large survey confirm the high prevalence, female preponderance and underrecognition of RLS in the general community. Although two thirds of patients had moderate-to-severe disease, none was on first-line treatment for RLS.

P220

Treatment of higher level gait disturbances with rivastigmine: A pilot study

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Background: Higher level gait disturbances (HLGD) are characterized by the combination of postural instability and exaggerated fear of falling. We propose that cognitive dysfunction may play a role in the development of HLGD.

Objectives: To evaluate the effects of acetyl choline esterase inhibitor (AChEI) Rivastigmine on gait and cognitive function in patients with HLGD.

Methods: Eleven non-demented patients (age 80.5 ± 5.9 , Mini Mental State Examination (MMSE) 28.4 ± 1.1) with HLGD were treated with increasing doses of rivastigmine for 12 weeks in an open label trial. Patients were assessed: at baseline, at weeks 4, 8, and 12 and 1 month after a washout period (week 16). At every visit, patients' subjective clinical global impression of change from baseline (SCGIC) and side effects were

recorded. At baseline, weeks 12 and 16, the assessment also included the MMSE, neuropsychological tests that evaluate attention, memory, and executive function (NeuroTrax Corp, NY), the Spielberger anxiety trait, the fear of falling questionnaire and gait assessment (speed, variability of the stride time and Timed Up and Go test (TUaG)). Wilcoxon Signed Rank tests were used to evaluate the effects of the intervention on each of the outcomes in a pair wise manner.

Results: Mean dose of rivastigmine was 6.8 mg/day. There was an improvement in TUaG test on week 12 (baseline: 14.9 ± 4.0 s vs. week 12: 13.4 ± 2.1 s, $P = 0.04$). Gait speed tended to improve at week 12 (baseline: 0.8 ± 0.2 m/s vs. week 12: 0.9 ± 0.1 m/s, $P = 0.09$). Cognitive tests showed improvement of composite scores for memory (88.5 ± 10.0 vs. 93.8 ± 6.1 ; $P = 0.01$). There was also a tendency for improvement in attention. At week 12, marked improvement was observed in the anxiety scores (36.4 ± 7.7 vs. 32.5 ± 7.8 ; $P = 0.01$) with subsequent returning to baseline (week 16: 37.0 ± 10.1). Overall SCGIC from baseline was positive in most of the patients on all visits, especially on week 8 and 12. Two patients reported worsening in SCGIC after washout period. Seven patients had to decrease the dose due to side effects.

Conclusion: Rivastigmine treatment is associated with improvement in mobility of patients with HLGD as well with some improvement in mental state. Larger, placebo-controlled studies are needed.

The study was partially supported by Novartis Israel Ltd.

P221

Paroxysmal dyskinesias and seizures associated with hemiplegic migraine: A report of three cases

S.A. Schneider, N.P. Quinn, R. Surtees, K.P. Bhatia (United Kingdom)

Objective: To report 3 patients with paroxysmal dyskinesia associated with hemiplegic migraine.

Background: Paroxysmal dyskinesias (PxD) are classified into the kinesigenic (PKD), non-kinesigenic (PNKD), and exercise-induced (PED) varieties. These have similarities with other episodic disorders identified to be channelopathies. Familial hemiplegic migraine (FHM) can be caused by mutation of the CACNA1A gene. The combination of FHM and PxD is rare.

Methods: Chart review.

Results: Clinical details of three patients (2F:1M) with PxD, generalized and/or absence seizures, and hemiplegic migraine are summarized. The average onset age of seizures was 13 months. Average age at onset of PED/PKD as well as hemiplegic migraine was 9 years. Family history was positive for classical migraine in all cases, but negative for seizures or PxD. PED/PKD attacks were induced by walking (1,2) and by sudden movement (3). Neurological examination was normal between attacks. Investigations for secondary dystonia, MRI scans and interictal EEGs were all normal. Brief case summaries:

Case 1: This 16-year-old girl had a generalised convulsion at 15 months after MMR vaccination. She had absence attacks from age 4 years. At 11 years she had migraine headaches with confusion, speech loss and hemiplegic weakness. The episodes lasted 20 min with full recovery. At age 12 years she began to have 4–5 PED attacks per month, abating after 5-min rest. There was a good response to sodium valproate, which had to be withdrawn due to side effects. Azetazolamide and phenytoin were tried with little success. **Case 2:** This 20-year-old woman had absence and generalized seizures from 10 months. From age 5 years she had PED attacks lasting for 30 min with full recovery. From age 8 years she had hemiplegic migraine episodes lasting 30 min. There was good response to combined lamotrigine, ethosuximide and sodium valproate. **Case 3:** This 17-year-old man had 20–30 PKD attacks per day, each lasting 10 s, from age 10 years. From age 13 years he had epileptic seizures. As a teenager he had migraine attacks with headache with facial or limb weakness, tingling, and confusion. Duration of attacks was one hour. There was good response to carbamazepine.

Conclusion: In rare instances PxD may be associated with hemiplegic migraine and seizures.

P222**Usefulness of video behavior recording in the diagnosis of restless legs syndrome in young children**

Y. Oka, T. Kadotani, H. Kadotani (Kyoto, Japan)

Objective: To analyze behavior of a familial case of probable restless legs syndrome (RLS) and its sibling, we used video-monitoring to clarify the characteristic RLS-related behavior. This could aid in diagnosing RLS in young children.

Background: It is difficult to diagnose RLS in children, because they may report RLS symptoms in different ways than adults. Diagnostic criteria for children relies on their description of symptoms, family history, and periodic limb movements. Additional behavioral analysis may be needed to certify the sensory symptoms of RLS for young children who may not have enough language ability.

Methods: 2 years 6-month-old and 5-month-old brothers whose father was diagnosed RLS were recruited. A neurology-sleep specialist confirmed that the elder brother fulfilled all the criteria for probable RLS through clinical interviews to the parents. Video recording was conducted for 4 nights for the elder brother and 2 nights for the younger brother. Recordings were reviewed by the specialist and RLS related behaviors were listed.

Results: The elder brother showed evening/nocturnal RLS behaviors such as unable to sit still and walk around while taking evening meal, put both legs in the duvet, frequently moves his lower extremity in the bed, walks out of bed often at bedtime, and unable to rest without being tapped on the legs by his mother. Periodic movements of the limbs were found in both children.

Conclusion: Video-recordings of the nocturnal behaviors clearly indicated the characteristic RLS features: worsening during rest, relief by movement, and worsening during night. Parents may not be able to properly recognize or describe the RLS-related behaviors. Thus, not only detailed clinical interviews to the parents, but also video-monitoring of the children to confirm their possible RLS-related behaviors could be beneficial to diagnose RLS in young children.

P223**The therapeutic reserve: Ropinirole in Parkinson's disease (PD)**

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Objective: To assess the titration of ropinirole over time in clinical trials.

Background: PD is a progressive neurological disorder. It is, therefore, important that the long-term management strategies used from first diagnosis of a patient allow treatment modification as symptoms worsen over time. Surveys in general practice often report that ropinirole is used at rather low doses, which are not consistent with those shown to be effective in clinical trials. The titration of ropinirole during its long-term use in clinical trials is reported here.

Methods: Dosing with ropinirole over time is reported from three long-term studies: a 3-year study (n = 335, Korczyn et al), the 2-year REAL-PET study (n = 186; Whone et al) and 5-year 056 study (n = 268; Rascol et al).

Results: An analysis of 6-month data from three trials of ropinirole as an initial therapy for PD showed that a dose of up to 9 mg/day was required to produce a first response (30% reduction in UPDRS motor score from baseline) in 75% of patients. In the 3-year trial, the mean dose of ropinirole at endpoint was 12.0 mg/day, which is 50% of the maximum recommended dose of 24.0 mg/day. In the REAL-PET study, mean dose of ropinirole after 2 years was 11.9 mg/day (50% max). During follow-up of patients from this trial, when receiving open-label therapies, the dose of ropinirole was titrated further to 13.4 mg/day after 4 years (56% max) in patients receiving ropinirole monotherapy, and 19.1 mg/day (80% max) for ropinirole in combination with L-dopa. In study 056, mean dose of ropinirole after 6 months was 10.1 mg/day (42% max). This dose increased steadily to 12.3 mg/day (51% max) at 2 years and 16.5 mg/day (69% max) at 5 years.

Conclusions: Ropinirole has a wide effective dosing range: a first response is seen in most patients at 6.0–9.0 mg/day, and the maximum dose

is 24.0 mg/day. Therefore, at most doses there is a large therapeutic reserve, with the potential to increase the dose to maintain optimal efficacy and tolerability. Ropinirole can also be titrated in increments to optimize efficacy throughout the disease course.

References

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P224**Hemifacial spasm: A clinical and epidemiological study in 208 patients**

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Background: Hemifacial spasm (HFS) is a frequent movement disorder, but only a few descriptive study on its clinical picture are currently available. In order to better characterize this condition, we designed a specific and detailed questionnaire on the clinical and epidemiological features of HFS.

Methods: Patients affected by HFS periodically attending three botulinum toxin clinics were interviewed during a 6-month period. Information was obtained by means of a standardized questionnaire administered face-to-face by a trained medical interviewer. Collected data included age, sex, disease duration, time range between the first symptoms and the correct diagnosis of HFS, family history, personal history of neurological disorders, and clinical features of the spasm with particular reference to distribution and occurrence of facial synkinesias and orbicularis oculi (OO) weakness.

Results: HFS was diagnosed in 208 subjects (79 men and 129 women, mean \pm SD age 65.6 ± 12.3 years) in accordance with published criteria. Mean disease duration was 10.2 ± 7.4 years. Latency between the first symptoms and the correct diagnosis of HFS was quite long (10.7 ± 7.4 years in primary HFS vs. 8.3 ± 7.1 years in secondary HFS, $P < 0.05$). In some cases the latency was up to 20 years. Family history of HFS was found in 7 cases, while a previous facial palsy was reported by 47 patients (secondary cases). HFS was left-sided in 112 patients, right-sided in 94 and bilateral in only 2. In the vast majority (156) of the cases the spasm was diffuse to the entire hemiface from the beginning, and only in 52 cases it was confined initially in the OO. Synkinesias were found in 99 cases and OO weakness in 67.

Conclusions: HFS is a common movement disorder but its clinical features are still not well known and therefore the correct diagnosis may be often overlooked. Familiar and bilateral cases are rare but not exceptional. Furthermore, the overlap in clinical features (including the occurrence of synkinesias and weakness) between primary and secondary cases is substantial, pointing out a common pathophysiological origin of the two forms.

P225**L-dopa effect on striatal DA shows a different pharmacokinetic for the neurotransmitter and the volume transmitter action of dopamine**

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Background: Levodopa remains the main stay treatment for Parkinson's disease (PD). A dual role of dopamine (DA) in the striatum as neurotransmitter (NT) and as volume transmitter (VT) is well recognized.

Objective: To define the central pharmacokinetics of levodopa on the NT and VT actions of DA.

Methods: Studies were performed in the striatum of the normal and 6-OHDA lesion rats. Two complementary methods were used: 1) Microdialysis to evaluate the extra-synaptic DA-pool (VT-role) and 2) microamperometry to evaluate the synaptic DA-pool (NT-role) following intraperitoneal administration of L-dopa plus benserazide.

Results: In normal rats, L-dopa induced a modest (\uparrow 200% for 100 mg/kg L-dopa) and slowly evolving (began at 60 min) effect on the extra-cellular extra-synaptic pool of DA (by microdialysis). In lesion animals, these effects

provoked by L-dopa were significantly increased (\uparrow 500%) and occurred much earlier (beginning at 20 min). On the other hand, L-dopa induced a marked (\uparrow 500% for 100 mg/kg L-dopa) and early (began at 20 min) replenishment of the synaptic DA-pool (measured by amperometry after electrical stimulation of the nigrostriatal tract). This effect was caused by the combined modification of DA-release (facilitated during the first 2 h) and DA-uptake (inhibited 2 h after L-dopa administration).

Conclusions: These data show a different pharmacokinetic for L-dopa action on the VT (began at 60 min and finished at 300 min; peak-response at 160 min) and NT (began at 20 min and finished at 250 min; peak-response at 50 min) roles of dopamine in the striatum. The L-dopa action on the VT role of DA increased and accelerated after DAergic denervation of the striatum.

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Gait and freezing in advanced Parkinson's disease: Response to pulsatile subcutaneous apomorphine stimulation

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Objective: We examined whether increase of dopaminergic stimulation improved the gait (freezing) in patients with advanced (PD).

Background: Degeneration of nigrostriatal neurons and deficiency of striatal dopamine produces many of the clinical manifestations of Parkinson's disease (PD). Postural instability in PD is notoriously refractory to levodopa treatment, implicating the involvement of nondopaminergic pathways. Late in the illness falls may occur either spontaneously or after minor perturbations. Walking, once underway, may be interrupted by further shuffling or even complete cessation of movement (freezing) if a doorway or other obstacle is encountered. Previous studies suggest that levodopa might actually increase the chances of falling, at least in advanced PD.

Methods: After informed consent was obtained, 10 patients with PD (mean duration of illness: 13.4 ± 3.2 years) chronically treated with levodopa and dopaminergic agonists (pramipexole, cabergoline, pergolide, or ropirinoles) were included for the study. All patients suffered motor fluctuations, dyskinesias and severe freezing. The UPDRS, tapping test of the limbs and freezing during the gait (time required to walk 20 m) were used for clinical assessment. Patients received subcutaneous apomorphine during "off" periods (mean dose: 4.5 ± 1.5 mg/4–5 times every day).

Results: With the introduction of apomorphine time "on" improved significantly. Freezing was not significantly modified and 4 patients showed a deterioration.

Conclusions: The neural mechanisms responsible for freezing remain poorly understood. In advanced PD the use of more intense dopaminergic stimulation may increase the postural abnormalities and freezing.

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Coverion from dopamine agonists to cabergoline: An open-label trial in 202 patients with advanced Parkinson's disease

G.J. Linazasoro, et al. (San Sebastian, Gipuzkoa, Spain)

Background: Small and one large clinical trials indicate that overnight switching from one agonist to another can be performed safely. Moreover, this may result in clinical benefits. This has not been demonstrated with cabergoline which long half-life could be a problem.

Objective: To determine safety and efficacy of overnight switching from dopamine agonists to cabergoline in patients with advanced PD.

Methods: 202 patients (mean age 67.6 years old, PD duration: 8.8 years) were included in this 12 weeks prospective, open-label, multicentric study. Efficacy was assessed by "on-off" diaries, UPDRS II and III, PDQ-8, sleep questionnaire and a new "ad hoc" scale to evaluate off period disability. Safety was assessed by using a check-list.

Results: All analysed parameters were significantly improved ($P < 0.0001$). Percentage of patients with moderate or severe disability during

off periods were reduced by half. Mean dose of cabergoline was 2.2 mg at the beginning and 3.2 mg at the end of the study. Levodopa dose remained unchanged. Twenty percent of patients reported side effects and 17 patients were withdrawn because of them (4 hallucinations, 2 vascular problems, 1 dyspnoea, 4 dizziness, 6 other causes).

Conclusion: Switching from one dopamine agonist to cabergoline in an overnight schedule is safe. The observed clinical improvement could be related to different factors.

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Body weight determines levodopa associated dyskinesia in Parkinson's disease

J.C. Sharma, M. Vassallo (Mansfield, Notts, UK)

Background: The factors known to lead to dyskinesia in Parkinson's disease are the disease duration and duration of levodopa therapy. Female patients are more prone to develop dyskinesia. We have retrospectively studied the possible additional factors, which might be implicated in the risk of developing dyskinesia.

Methods: A cohort of PD patients was assessed at initial presentation and periodically for the standard measurement scales in addition to the development of dyskinesia. A detailed account was made of the levodopa and other drug therapy.

Results: 286 patients assessed at the first presentation and 224 at the second presentation, the follow-up was up to 7 years. There was a significantly higher incidence of dyskinesia in females at the second assessment—32% vs. 20%, $P < 0.05$. The dyskinetic patients, both male and female, had received significantly higher maximum level dose of levodopa (656 ± 327 mg vs. 513 ± 395 , $P < 0.01$) in addition to longer duration of PD (10 ± 4 vs. 6.4 years). Final levodopa dose was lower in both groups but still higher in dyskinetic patients: 503 ± 269 vs. 448 ± 294 mg. Additionally, the dyskinetic patients had a significantly lower body weight— 67 ± 15 kg vs. 75 ± 15 kg, $P < 0.013$ from the initial assessment and had further weight loss during follow up, final mean weight being 65.3 ± 16 vs. 76.8 ± 14 kg, $P < 0.001$. The dyskinetic patients received higher dose per kilogram body weight irrespective of gender: 9.8 mg vs. 6.8 mg per kilogram at the maximum dose level. Logistic regression and correlation coefficient analyses revealed weight and high levodopa dose to be the only independent significant factors for dyskinesia. Dyskinetic patients were more often treated with dopamine agonists for their levodopa sparing property, $P < 0.001$.

Conclusion: Dyskinesia seems to be related to the dose of levodopa and the body weight, lower weight predisposes to dyskinesia. Levodopa dose should be adjusted according to the patients' weight, lower weight patients should be prescribed a lower dose. Our data recommends a dose of 6 to 8 mg levodopa per kilogram body weight to prevent development of dyskinesia. Low body weight patients should be preferentially targeted for non-levodopa drugs to control symptoms related to Parkinson's disease with a view to use a lower levodopa dose. This hypothesis should be tested in prospective trials.

P229

Can chronic subthalamic nucleus stimulation induce de novo tremor in Parkinson's disease?

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Background: Subthalamic nucleus (STN) stimulation dramatically improves parkinsonian symptoms notably the tremor. The occurrence of a tremor in the first 6 months following the surgical procedure, in Off medication and Off stimulation condition, in patients without tremor Off medication preoperatively is much less common.

Case report: We report the cases of 3 patients who presented this modification of symptomatology 6 months after STN stimulation.

Patient 1: This right-handed man was diagnosed with PD when he was 48 years old. He had no past medical history. The first symptom was bradykinesia of the right hemibody without any tremor. Levodopa was introduced one year after disease onset and the improvement was major.

Motor fluctuations appeared 6 years later and dyskinesias began 10 years after PD onset. Due to the worsening of motor signs subthalamic nucleus (STN) stimulation was implanted after 11 years disease evolution, under local anaesthesia and stereotactic guidance as previously described. The electrodes were connected to a pulse generator (Kinetra or Itrell II, Medtronic, Minneapolis, MN, USA). Before surgery his treatment consisted in: levodopa: 1700 mg/D □ ropinirole: 22 mg/D □ amantadine: 200 mg/D □ entacapone: 1400 mg/D. In the Off medication condition no tremor was present. Six months after surgery, motor fluctuations and dyskinesias considerably improved and the treatment was dramatically reduced to ropinirole 15 mg/D and levodopa: 400 mg/D. However, in the off drug and off stimulation condition, the patient developed tremor, which was absent off medication before surgery. This tremor predominated on the right hemibody and on the upper limb. The tremor was present at rest but also during posture. Two other cases are presented.

Conclusions: Several hypotheses can be evoked. First, it could be argued that the important reduction of dose of antiparkinsonian drugs after surgery could have unmasked the tremor, which was already present preoperatively. Second, chronic STN stimulation could have induced profound modifications of neuronal activity and have led to a tendency after stimulation arrest for STN, Gpi or thalamic cells, to display low frequency oscillatory activity like tremor-cells.

P230

Dopamine agonist pergolide prevents levodopa-induced quinoprotein formation in parkinsonian striatum and shows quenching effects on dopamine-semiquinone generated *in vitro*

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Objective: To clarify the effects of a dopamine (DA) agonist pergolide on levodopa-induced elevation of quinone bodies, we examined striatal changes in quinoprotein, which represents generation of DA quinones, using hemi-parkinsonian model mice. Moreover, the *in vitro* quenching effects of pergolide on DA quinones were also accessed to elucidate its neuroprotective property against DA quinone-induced neurotoxicity.

Background: The antioxidant and neuroprotective properties of pergolide have been revealed in our previous reports (Arch Int Pharmacodyn Ther 1995;329:221; J Neurochem 1996;67:2208; Brain Res 1998;790:202). The neurotoxicity of DA quinones that appears DAergic neuron-specific oxidative stress has recently been known to play a role in the pathogenesis and/or progression of Parkinson's disease and neurotoxin-induced parkinsonism (Neurotoxicol Res 2003;5:165).

Methods: We measured changes in quinoprotein, which represents generation of DA quinones, in the striatum after repeated administration of pergolide (0.5 mg/kg/day, 7 days) and/or levodopa/carbidopa (50/5 mg/kg/day, 7 days) using 6-OHDA-lesioned hemi-parkinsonian mice. Moreover, the effects of pergolide on DA-semiquinones were also evaluated using an *in vitro* DA-semiquinone generating system and electron spin resonance methods.

Results: Striatal quinoprotein levels were elevated specifically in the parkinsonian side after the repeated levodopa administration. The levodopa-induced increase in the striatal quinoprotein contents was almost completely suppressed by co-administration with pergolide in the lesioned side, but not in the non-lesioned side. Furthermore, it was clarified that pergolide scavenged DA-semiquinones generated *in vitro* in a dose-dependent manner.

Conclusions: The present study revealed that cytotoxic quinone generation was markedly increased in excessively levodopa-administered parkinsonian striatum and was dramatically prevented by the treatment of pergolide, which has quenching effects on DA-semiquinone as DAergic neuron-specific oxidative stress. These suppressive and quenching effects of pergolide against cytotoxic DA quinones may play a key role in its neuroprotective mechanism in the parkinsonian brain.

P231

Olfactory testing in Parkinson's disease and other movement disorders: Correlation with Parkinsonian Severity

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Objective: Screen for olfactory dysfunction in a cohort of prospective brain donors.

Background: Olfactory dysfunction (odor detection) in Parkinson's disease (PD) has been independent of disease severity, normal in restless legs syndrome (RLS), and conflicting data is available for essential tremor. This study extends previous work in an elderly cohort of patients and controls.

Methods: As part of an ongoing brain donation program subjects performed the 40 question UPSIT. Subjects are categorized as clinically possible PD (bradykinesia or rest tremor), clinically probable PD (2/3 clinical signs of PD), tremor disorder (at least a +1 postural or kinetic tremor with no apparent symptomatic etiology), essential tremor (at least +2 postural or kinetic tremor that is bilateral, long-standing), restless legs syndrome, or control.

Results: Based on previously published categories, in the control population (n = 155) 22.6% were normosmic, 31.6% had mild hyposmia, 18.1% had moderate hyposmia, 12.3% severe hyposmia, 14.8% anosmia. A correlation of UPSIT data with age reveals a r of -0.38 (-0.51 to -0.24 95%CI). The results of the UPSIT revealed the probable PD group (22.4 ± 8.9) had olfactory dysfunction compared with the controls (29.1 ± 7.8, P < 0.001). The possible PD group (27.0 ± 6.7) was higher than the probable PD group (P = 0.01) but not different from controls (P = 0.66). Based on the most recent visit, there was an inverse correlation between UPDRS motor score and the UPSIT score for both the possible PD (r = -0.46, 95% CI -0.76 to -0.01, n = 19) and probable PD (r = -0.54, 95% CI -0.74 to -0.25, n = 35). UPSIT scores for essential tremor (29.12 ± 6.77, n = 26), tremor disorder (27.42 ± 7.49, n = 53), and RLS (29.40 ± 7.17, n = 35) did not differ from controls.

TABLE 1. Abstract 231: UPSIT scores

Subject group	n	Age, mean (SD)	UPSIT, mean (SD)
Control	155	77.9 (8.6)	29.1 (7.8)
Clinically possible PD	35	79.3 (5.8)	27.0 (6.7)
Clinically probable PD	55	79.2 (8.6)	22.4 (8.9)*
Essential Tremor	26	80.7 (7.4)	29.1 (6.8)
Tremor disorder	53	81.8 (7.4)	27.4 (7.5)
RLS	35	76.2 (10.5)	27.4 (7.2)

*P < 0.001.

Conclusions: UPSIT scores are low in clinically probable PD cases and inversely correlated with PD severity in clinically probable and clinically possible PD. UPSIT is normal in RLS and essential tremor.

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Olfactory dysfunction in Parkinson's disease using the Brief Smell Identification Test: Early Alert™

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Objective and Background: There has been an increase of interest in olfactory dysfunction since it was realized that anosmia was a common feature of idiopathic Parkinson's disease (IPD). To date, there are no studies on olfaction in parkinsonism in Korea. This study aimed to reinvestigate the diagnostic value of olfactory testing for odor identification and to compare olfactory function in IPD and atypical Parkinson's syndrome (APS). Furthermore, we sought to assess whether olfactory function differed in early-onset Parkinson's disease (EOPD) compared with late-onset Parkinson's disease (LOPD).

Methods: Thirty-nine patients with parkinsonism (17 males and 22 females) and 29 control subjects (15 males and 14 females) were tested. The olfactory function tests we used are 12-item brief smell identification test (Early Alert™; FMG Innovations, Inc, USA). Brief smell identification test (B-SIT) kit was presented and the subjects were asked to identify them. Using a multiple forced choice design identification of 12 common odors was performed with a list of 4 descriptors. B-SIT score was the number of incorrect answers.

Results: The mean B-SIT score in parkinsonism ($n = 39$) was 6.9. This was higher than the normal group ($n = 29$) mean of 3.5 ($P < 0.0001$), whereas the mean B-SIT score in IPD ($n = 29$) did not differ from the APS group ($n = 10$) (mean 7.0 vs. 6.7; NS). 9 of the 12 B-SIT odors (cinnamon, turpentine, lemon, chocolate, rose, pineapple, gasoline, soap, onion) were required to adequately discriminate patients with parkinsonism from controls. In addition, the EOPD group ($n = 10$) was higher than the LOPD group ($n = 9$) but difference was not significant (mean 7.5 vs. 6.7; NS).

Conclusion: Odor identifications were severely disturbed in patients with parkinsonism when compared to control subjects. According to onset time, olfactory function disturbed in EOPD compared with LOPD, so further study need to be identified in EOPD on olfaction.

P233

Intake of vitamin E, vitamin C, and carotenoids and the risk of Parkinson's disease: Systematic review and meta-analysis of observational studies

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Objective: To assess the impact of vitamin C, vitamin E, and beta-carotene intake on the risk of developing PD.

Background: Observational studies have suggested that diets rich in antioxidants may reduce the risk of developing Parkinson disease (PD).

Methods: We did a meta-analysis of observational studies using Medline (1966 through March 2004), Embase (1980 to March 2004) and the Cochrane Library (issue 1, 2004). We entered medical subject heading terms including *antioxidants, diet, vitamin C, ascorbic acid, vitamin E, tocopherols, beta carotene, and flavonoids*. We combined the results of this search with the term *Parkinson disease*. We retrieved all relevant articles and searched reference lists of retrieved articles to find other relevant articles. Studies were included if they had: 1) a clear definition of exposures, that is intake of vitamin C, vitamin E, and beta-carotene; 2) clear diagnostic criteria for PD; 3) controlled for potential confounders using appropriate statistical techniques; and 4) provided odds ratios (ORs) or relative risks (RRs). Log RRs for cohort studies or ORs were weighed by the inverse of their variances to obtain a pooled measure of the RRs. We tested for heterogeneity using the bootstrap version of the DerSimonian and Laird Q^* statistic (with 1000 replications) as well as graphically using the Odd man out plot. We also quantified heterogeneity using the I^2 statistic.

Results: Eight studies were identified (six case-control, one cohort, and one cross-sectional). These studies suggest that dietary intake of vitamin E protects against the development of PD. This protective influence was seen with both moderate intake (relative risk (RR) 0.81, 95% confidence interval (CI) 0.67–0.98) and high intake (RR 0.78, 95% CI 0.57–1.06) of vitamin E. The studies did not suggest any protective effects associated with vitamin C or beta-carotene.

Conclusions: Diets rich in vitamin E appear to lower the risk of developing PD. It is not clear whether vitamin supplements confer the same benefit as dietary sources. Dietary intake of vitamin C and beta-carotene does not appear to influence the risk of developing PD. These results require confirmation in randomized controlled trials.

P234

Dissociation of cardinal motor signs in Parkinson's disease

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Objective: Most of cardinal motor signs are pronounced on the same side. But we can unusually find one type of cardinal motor sign that is pronounced in one side and other motor signs are pronounced in contralateral side. The dissociation of motor signs is rarely observed.

Background: Although a uniform clinical definition of Parkinson's disease (PD) has been established, most movement disorder specialists consider the presence of two of three cardinal motor signs (tremor, rigidity, bradykinesia) and a consistent response to levodopa. The asymmetrical onset of cardinal features has been proposed as a criteria for diagnosis of PD.

Methods: To determine the frequency of dissociation of asymmetry, we examined subjects who were clinically diagnosed as PD and visited Korea University Guro Hospital for at least 6 months between March 2003 and July 2004. Clinical characteristics for each patient during each follow-up visit were analyzed based on the Unified Parkinson's Disease Rating Scale (UPDRS).

Results: Dissociation of asymmetry of cardinal motor signs was noted in 9 (10.6%) of the 85 patients. This pattern was manifest at initial presentation and persisted until the end of follow-up. Six patients showed the dissociation of tremor side and rigidity-bradykinesia side. Two patients showed the dissociation of bradykinesia side and rigidity-tremor side. One patient showed the dissociation of rigidity side and bradykinesia-tremor side. One patient in non-dissociation group showed rest tremor pronounced in one upper limb and contralateral lower limb. There were no differences between dissociation group and non-dissociation group in demographic factors. The changes of scores of UPDRS part 1, 2, 3 during the 6-month follow-up period were not different between two groups.

Conclusions: The dissociation of motor cardinal signs occurred in 10.6% of PD patients in our clinic. We thought that each cardinal motor signs have different pathogenesis and anatomical bases. The presence of dissociation of cardinal motor signs did not affect the natural history of PD.

P235

Cortical dysplasia and hemiparkinson-hemiatrophy syndrome

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Background: Hemiatrophy is related to a variety of neurologic conditions. Increasingly, malformations caused by abnormalities of cortical development are being recognized in patients with drug-resistant epilepsy. Hemiparkinson-hemiatrophy (HP-HA) syndrome is a rare form of secondary parkinsonism that is characterized by a slow progressive course, early age of onset, and early premedication dystonia. We describe an HP-HA patient with cortical dysplasia.

Case report: A 19-year-old left-handed man presented with a gait difficulty present since he was young and a 3-year history of right-hand slowness. On examination, there was no facial asymmetry. The difference in circumference was 2 cm (27 vs. 29 cm, right vs. left) for the forearm and 4 cm for the distal (40 vs. 44 cm) and proximal (59 vs. 63 cm) leg. From bone scanography, the difference in tibia length was 1.5 cm (33.0 vs. 34.5 cm) and in femur length was 1.9 cm (40.2 vs. 42.1 cm). There was rigidity and bradykinesia of the right extremities, but no tremor (UPDRS motor score 19). There was no dystonia at rest, but while walking, there was dragging of the right leg with foot inversion and dorsiflexion, and dystonic posturing of the right hand. The EEG and the plasma copper and ceruloplasmin levels were normal. Brain MRI showed cortical atrophy of the left hemisphere and ventricular asymmetry. The fast inversion recovery image showed marked cortical dysplasia of the right hemisphere. Brain SPECT revealed marked asymmetry in temporal and parietal lobe perfusion. Levodopa/carbidopa was started at a dose of one 100/25-mg tablet, three times a day. After treatment, there was improvement of the bradykinesia and dystonia on walking. We re-examined his symptoms using UPDRS, and the motor score was 11. Now, the patient is able to make pottery at school while taking Levodopa/carbidopa 100/25 mg, three times a day.

Conclusions: Our patient clearly demonstrated unilateral parkinsonian symptoms, including bradykinesia, rigidity, unilateral exertional hand dystonia, and asymmetry of his brain and extremities. Interestingly, the neuroradiological features showed poor differentiation between the white and gray matter, suggesting abnormal cortical development. To our knowledge, this is the first report of HP-HA in a patient with cortical dysplasia.

P236**Caspase-11, IL-1 β and microglial activation mediate LPS-induced substantia nigral dopaminergic neurotoxicity in mice**

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Objective: To examine the mechanism of substantia nigral (SN) dopaminergic neurotoxicity by lipopolysaccharide (LPS).

Background: The endotoxin lipopolysaccharide (LPS), a component of the Gram-negative bacterial cell wall, selectively induces degeneration of substantia nigral (SN) dopaminergic neurons via activation of microglial cells in rats and mice. It is recently reported that long-term stimulation of innate immunity by systemic injection of LPS exacerbates motor neurodegeneration in a mouse model of amyotrophic lateral sclerosis (ALS), suggesting that the endotoxin LPS could be involved in neurodegenerative diseases caused by chronic peripheral bacterial infections especially in the presence of genetic or environmental risk factors. Then, caspase-11 plays a crucial role in LPS-induced septic shock in mice. So we examined the mechanism of LPS neurotoxicity on SN dopaminergic neurons in C57BL/6 mice and caspase-11 knockout mice.

Methods: Mice were stereotaxically injected with LPS into the SN on one side and vehicle into the SN of the other side. Immunohistochemistry, Western blotting analysis, ELISA, and RT-PCR were performed to evaluate damage of SN dopaminergic neurons and activation of microglial cells.

Results: Intranigral injection of LPS at 1 or 3 $\mu\text{g}/\mu\text{L}/\text{site}$ decreased tyrosine hydroxylase (TH)-positive neurons and increased microglial cells in the SN compared with the contralateral side injected with vehicle, at days 7 and 14 post-injection in C57BL/6 mice. Intranigral injection of LPS at 3 $\mu\text{g}/\mu\text{L}/\text{site}$ induced the expression of caspase-11 mRNA in the ventral midbrain at 6, 8 and 12 h post-injection by RT-PCR, and the expression of caspase-11 in the SN at 8 and 12 h post-injection by immunohistochemistry and/or Western blotting analysis. Moreover, LPS at 3 $\mu\text{g}/\mu\text{L}/\text{site}$ increased IL-1 β content in the ventral midbrain at 12 and 24 h post-injection by ELISA. LPS failed to elicit these responses in caspase-11 knockout mice.

Conclusions: Our results indicate that the neurotoxic effects of LPS on nigral dopaminergic neurons are mediated by microglial activation, IL-1 β , and caspase-11 expression in mice.

P237**Conversion from sustained release carbidopa/levodopa to Stalevo[®] in Parkinson's disease patients**

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Objective: To determine if the conversion from sustained release carbidopa/levodopa with or without entacapone to Stalevo improves motor functioning and quality of life in Parkinson's disease (PD) patients.

Background: There is currently no information on the benefits and potential side effects related to converting patients suboptimally controlled on sustained release carbidopa/levodopa to Stalevo.

Methods: PD patients reporting suboptimal symptom control with sustained release carbidopa/levodopa were converted to Stalevo. In general, each sustained release 50/200 was converted to Stalevo 150 and each sustained release 25/100 was converted to one Stalevo 100. Additional adjustments were made as necessary. Prior to conversion, patients were assessed with the full UPDRS and PDQ-39 quality of life assessment. After one month on Stalevo these assessments were repeated and patients were queried as to which treatment they preferred.

Results: There were 56 patients with an average age of 68 years and an average disease duration of 11 years. Forty-four patients completed the study. Twelve patients withdrew from the study prior to 1 month due to adverse effects from Stalevo including dizziness, nausea, vomiting, and increased off time or dyskinesia. None of these patients had been previously exposed to entacapone. Of those that completed, 84% preferred Stalevo [25 better control, 8 more convenient, 3 cost, 1 works faster]. In this group, UPDRS mentation and motor scores as well as total PDQ-39 quality of life scores were significantly improved. Six patients had a reduction in dyskinesia, 25 were unchanged and 6 were worsened. Off time was reduced in 12 patients, unchanged in 21 and worsened in 4. The

remaining 16% preferred sustained release carbidopa/levodopa [5 better control, 1 fewer AEs, 1 works faster]. Dyskinesia was improved in 1 patient and unchanged in 6 and off time was reduced in 2, unchanged in 2 and worsened in 3 with Stalevo. There were no significant changes in UPDRS scores for this group.

Conclusion: A majority of patients suboptimally controlled on sustained release carbidopa/levodopa can be converted to Stalevo resulting in improved motor control and quality of life. However, patients not previously exposed to entacapone may have fewer side effects if entacapone is added prior to an attempt to convert to Stalevo.

P238**Parkinson's disease in Africa: A systematic review**

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Objective: To systematically review publications on PD in Africa, with emphasis on epidemiological and genetic studies.

Background: Parkinson's disease (PD) occurs worldwide, but little is known about PD in Africa.

Methods: Articles published before July 2004 were identified using several strategies. These included searches of Medline, using the terms (Parkinson's disease; parkinsonism; paralysis agitans; movement disorders; epidemiology and Parkinson's disease; or genetics and Parkinson's disease) $\times \times$ Africa.

Results: The studies emanated from 13 African countries (Kenya, Uganda, Tanzania, Ethiopia, Nigeria, Senegal, Ghana, Togo, Libya, Tunisia, Algeria, Zimbabwe, and South Africa) with the first report in 1944. The publications fell into four categories: hospital-based descriptions (n = 17), prevalence studies (n = 7), incidence studies (n = 1), and genetic studies (n = 3). While diagnostic criteria were not standardized for the hospital-based studies, they documented the occurrence of PD in Africa, described its clinical characteristics, and conveyed the impression that PD is less common in Black Africans. The prevalence studies revealed intra-continental geographic variation in PD prevalence. There were lower prevalence rates from sub-Saharan Africa (e.g., 59/100,000 in Nigeria) compared to North Africa (e.g., 216/100,000 in Tunisia). However, age and sex-adjusted comparisons of the two prevalence estimates is not possible. The single incidence study of PD was conducted in Benghazi, Libya, and reported a crude incidence rate of 4.4/100,000 per year. These prevalence and incidence rates appear lower than those reported for European and North American populations. Few genetic studies of PD have been reported from Africa, and none in Blacks. One study described the inheritance patterns of PD in 21 Tunisian families, a second reported clinicopathological characteristics in a Tunisian family with a PARK2 mutation, and a third confirmed linkage of autosomal recessive juvenile onset parkinsonism to the PARK2 locus in one Algerian family. There are no case-control or cohort studies of PD reported from Africa.

Conclusions: This review provides a summary of PD research in Africa over the past 60 years and highlights the information gaps and potential areas for future research.

P239**Bilateral improvement after unilateral subthalamic nucleus stimulation in a patient with advanced Parkinson's disease**

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Objective: To describe a patient with advanced PD who showed marked improvement of bilateral parkinsonian features after unilateral deep brain stimulation (DBS) of the subthalamic nucleus (STN) during the follow-up period of 9 months.

Background: STN-DBS has become an increasingly important treatment of advanced Parkinson's disease (PD). Although bilateral STN-DBS has been reported to improve most of parkinsonian motor features, little is known about the clinical outcome of unilateral STN-DBS.

Methods: The clinical features, disease evolution, and response to treatment were described. The video of the parkinsonian features before and after unilateral STN-DBS will be demonstrated.

Results: A 53-year-old woman first developed left leg tremor in 1995 and was diagnosed with PD in 1998. The patient was adequately controlled with the available pharmacological therapy but developed motor fluctuation followed by dyskinesia developed in 2002. In December 2003, she had undergone surgery for STN-DBS, when her motor scores on UPDRS were 12.5 when on and 69 when off and ADLs scores (UPDRS II) were 3 when on and 36 when off. Microelectrode recording was carried out for accurate targeting during surgery. At 3 months postoperatively, the patient showed a marked improvement in bradykinesia, rigidity, tremor, gait freezing, and dyskinesia. The on-period UPDRS III scores of the patient were not changed (from 12.5 to 12.5), but the off-period scores strikingly improved (from 69 to 22.5). Although the greatest improvement occurred on the side contralateral to the electrode, interestingly, significant ipsilateral improvement of tremor, rigidity and bradykinesia was also observed. Bilateral anti-parkinsonian effect lasted during the follow-up period of 9 months.

Conclusions: Our patient suggests that unilateral STN-DBS may provide a significant bilateral anti-parkinsonian effect in advanced PD. The mechanism of the bilateral anti-parkinsonian effect after unilateral STN-DBS may be related to the bilateral organization of the cortico-striatal projection fibers.

P240

Factors related to quality of life in patients with Parkinson's disease

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Objective: To investigate QOL and related factors in Parkinson's disease (PD) patients in Korea.

Background: PD is the most common neurodegenerative movement disorder. The goal of therapeutic interventions for PD is to manage the symptoms and mitigate the effect on the quality of life (QOL) in the individual patient.

Methods: Between January 1, 2004 and July 15, 2004, 81 patients with PD were included. Patient data concerning demographics and social status and disease characteristics were obtained. The patients were assessed using Hoehn and Yahr stage (HY), Schwab and England activities of daily living (ADL) score, Unified Parkinson's Disease Rating Scale (UPDRS), Parkinson's disease quality of life (PDQL), Modified Beck Depression Inventory (BDI), and Mini-Mental State Examination (MMSE).

Results: Twenty-five male and 56 female patients were included. The mean age was 60.7 years. The mean disease duration was 7 years, and the mean age at onset was 54.1 years. Among the demographic data, the male patients ($P = 0.07$) and young age at onset ($P = 0.07$) showed borderline correlation with higher PDQL score. Medical cost for PD ($P < 0.001$) showed significant correlation with PDQL score. The patients working in the daytime or spending the daytime with spouse showed significantly higher PDQL score than the others ($P = 0.01$). Among the disease characteristics, the disease duration ($P < 0.001$), levodopa dosage ($P < 0.001$), UPDRS I, II, III, IV and total score ($P < 0.001$), ADL ($P < 0.001$), HY stage ($P < 0.001$), presence of motor fluctuation ($P < 0.001$), dyskinesia ($P < 0.001$), and depression ($P < 0.001$) had a strong correlation with the PDQL score. However, PDQL score was not affected by the patient's age, educational level, income, marital status, occupation, person living together, religion, frequency of hospital visits, area of living, and MMSE score. On stepwise regression analysis, the most important factor related to PDQL score was presence of depression ($P < 0.001$), disease duration ($P < 0.001$) and the UPDRS total score ($P < 0.05$) in order of strength.

Conclusions: The QOL in patients with PD was strongly associated with depression, disease duration, and the severity of PD. We suggest that the evaluation and proper management of depression as well as PD symptoms is necessary to improve the QOL of PD patients.

P241

The tolerability of ACP-103, a 5-HT_{2A} receptor inverse agonist in Parkinson's disease patients

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Objective: To develop a novel agent for treatment-induced dysfunction in Parkinson's disease (PD).

Background: Treatment limiting side effects, including psychosis and dyskinesias, occur in a majority of PD patients during the course of treatment of this illness. Atypical antipsychotics, often used in low doses, are the currently preferred option for the treatment of drug-induced psychosis in PD patients, yet motoric intolerance of these agents occurs frequently. ACP-103 is a 5-HT_{2A} receptor inverse agonist devoid of any dopaminergic receptor activity, which may find utility as a potential therapeutic agent for treatment-induced dysfunction in PD. We sought to demonstrate the safety, tolerability, and pharmacokinetics of ACP-103 in PD patients.

Methods: We conducted a randomized, double-blind, placebo-controlled, multiple oral dose escalation study in PD patients. The patient population included male and female subjects of any age with a clinical diagnosis of idiopathic PD. **Results:** A total 12 patients, ranging in age from 47 to 78 years, were included, with 4 subjects randomized to active drug and 2 randomized to placebo for each of 2 dose levels (25 mg and 100 mg) of ACP-103, administered orally once daily for 14 days. All 12 subjects completed the study. ACP-103 was found to be safe and well tolerated, and there were no drug-related serious adverse events reported. Importantly, ACP-103 did not worsen the pre-existing motor deficits in these patients. Further, the pharmacokinetics observed in PD patients were comparable to those observed previously in healthy normal volunteers.

Conclusions: ACP-103 appears to be safe and well tolerated in PD patients, and is currently being studied in Phase II trials as a novel treatment for psychosis and dyskinesias in PD patients.

P242

Long-term benefits of rivastigmine in dementia associated with Parkinson's disease: An open-label extension study

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Objective: To determine whether treatment benefits of rivastigmine in patients with dementia associated with Parkinson's disease (PD) were sustained over the long term.

Background: In patients with dementia associated with PD, the short-term efficacy and safety of rivastigmine, an inhibitor of acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE), were previously demonstrated in a 24-week, double-blind, placebo-controlled trial.

Methods: Following the double-blind trial, all patients were permitted to enter the open-label extension, during which they received rivastigmine 3–12 mg/day. All patients were re-titrated to maximum tolerated doses. Patients were assessed at week 24 (end of double-blind phase) and week 48 (end of open-label phase).

Results: Of the 433 patients who completed the double-blind trial, 334 entered, and 273 completed, the open-label extension. The mean Alzheimer's Disease Assessment Scale cognitive subscale (ADAS-cog) score at the end of the double-blind phase was 3.3 points above baseline for the rivastigmine group and 0.5 points below baseline for the placebo group. At the end of the open-label extension, ADAS-cog scores were maintained 2.0 and 2.2 points above baseline for original rivastigmine and placebo groups, respectively. Thus, placebo patients switching to rivastigmine for the open-label phase experienced a mean cognitive improvement similar to that of the patients in the original rivastigmine group during the double-blind phase. No new safety or tolerability problems emerged with long-term rivastigmine treatment in this population.

Conclusions: Long-term rivastigmine treatment appears to be well tolerated and may provide sustained benefits in patients with dementia associated with PD who remain on treatment for up to 48 weeks.

P243

Do patient outcomes predict caregiver depressive symptoms?

M. Trail, K. Cook, N.D. Nelson, E.C. Lai (Houston, Texas, USA)

Objective: To investigate the impact of several patient-reported quality of life variables on caregiver self-reports of depressive symptoms.

Background: Evidence mounts that physical activity improves the health and quality of life of persons with chronic illnesses. Little research has examined the relationship between caregiver depression and patient health status and health behaviors.

Methods: A cross-sectional survey design was conducted at the Houston VA Parkinson's Disease Research, Education and Clinical Center (PADRECC). A convenience sample of 61 pairs of patients and caregivers completed study measures. The dependent measure was caregiver reports of depressive symptoms as measured using the Center for Epidemiologic Studies-Depression Scale (CES-D). Explanatory variables included patient's ADL health status, self-reported physical activity, and patients' CES-D scores. Predictive models were compared using multiple regression.

Results: Patients' self-reported physical activity was the best predictor of caregiver CES-D scores (higher activity was associated with lower CES-D scores). Including patient ADL health status or patient CES-D or both in the predictive model did not account for a significantly greater amount of variance in caregiver CES-D scores.

Conclusions: Of the variables evaluated, patients' self-reported activity was the best predictor of caregiver reported depressive symptoms. It cannot be concluded from these results that increased physical activity in persons with PD results in less depression among caregivers. This association is intriguing, however, and warrants continued research. Future studies should evaluate the impact of exercise interventions on the quality of life of persons with PD and their caregivers.

P244

Ambulatory automatic assessment of motor fluctuations in Parkinson's disease

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Objective: The aim of this study was to develop an algorithm that is able to distinguish between "on" and "off" states in patients with Parkinson's disease during daily life activities.

Background: Motor fluctuations constitute a major problem in the long-term management of PD and add substantially to the patient's disability. Self-report of the motor-state in diaries has several limitations and can be troublesome or even unreliable. Therefore, automatic ambulatory assessment of the motor state and motor fluctuations would be highly useful in the management of PD and in the evaluation of surgical and pharmacological interventions.

Methods: 23 patients were continuously monitored in a home-like situation for a period of approximately 3 h. During this 3-h period, the patients performed about 35 functional daily-life activities. Behavior and comments of patients during the experiment were used to indicate the "on" and "off" periods by a trained observer. Behavior of the patients was measured using triaxial accelerometers, which were placed at 6 different positions of the body. Several parameters related to hypokinesia (percentage movement), bradykinesia (mean velocity) and tremor (percentage peak frequencies above 4 Hz) were used to distinguish between "on" and "off" states. The on-off detection was evaluated using the sensitivity and specificity, which were defined as the fraction of correctly classified data in the "off" and "on" state, respectively. The performance for each patient was defined as the average of the sensitivity and specificity.

Results: The best performance to classify "on" and "off" states was obtained by analysis of movements in the frequency domain with a sensitivity of 0.97 and a specificity of 0.97. Thirteen out of 22 patients showed a performance exceeding 0.97. Only one patient showed a performance smaller than 0.90 (0.89).

Conclusions: We have developed an automatic, unsupervised algorithm, which can distinguish between "on" and "off" states with a sensitivity and specificity near 0.97. This method can automatically assess the motor state

of PD patients and can operate successfully in unsupervised ambulatory conditions.

P245

Do Parkinson's disease caregiver proxy reports represent patient self-reports?

N.D. Nelson, K. Cook, M. Trail, E.C. Lai (Houston, Texas, USA)

Objective: To compare Parkinson's disease (PD) caregiver proxy reports with patient self-reports of quality of life (QOL) and physical activity.

Background: Agreement between patient and proxy reports has been studied in patients with specific diseases, but less so in PD. One PD study examined concordance on established measures of PD staging and a second study explored agreement on QOL. Concordance was influenced by the physical presence of caregivers in the first group and by the concrete responses and PD subgroups in the second group.

Methods: A cross-sectional survey design was conducted at the Michael E. DeBakey VA Parkinson's Disease Research, Education and Clinical Center (PADRECC). QOL was measured using the PDQ-39 and the frequency of exercise during the past week was measured by three items. Descriptive statistics were collected for age, HY stage, Schwab and England (SE) score, and all study measures. Confidence intervals (95%) were calculated for scores on all self-report measures. An intraclass correlation coefficient was calculated to estimate inter-rater reliability of patient and proxy responses and to compare responses by subgroups.

Results: A total of 64 patient-proxy pairs participated in this study. Over 90% of the proxies were spouses. The mean age was 74.41. The mean HY score was 2.87 and the mean SE score was 74.89. None of the differences between proxy and patient reports were statistically significant ($P = 0.05$). On average, proxies rated patient disability higher and QOL lower than did patients. Although the frequency of physical activity is more objective than the domains measured by the PDQ-39, we obtained greater patient-proxy agreement for the PDQ-39 subscales than for the physical activity items.

Conclusions: Our results are consistent with other findings where proxies tend to rate patient disability higher than the patients, and rate patient's QOL lower than do patients. Because congruence may be lower with more impaired patients, future research may address whether these differences by subgroups influence patient-proxy agreement. Proxy reports may diverge appreciably from patient self-reports. These differences should be considered when considering innovative research designs for proxy and self-reports that affect clinical outcomes.

P246

The effects of expiratory muscle strength training program on pharyngeal swallowing in patients with idiopathic Parkinson's disease

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Objective: This study investigated the effects of a rehabilitative program for the respiratory muscles on selected temporal and displacement measures of thin liquid swallowing in patients with moderate idiopathic Parkinson's disease (IPD).

Background: Respiratory dysfunction is a common comorbidity of IPD. Aspiration pneumonia holds the highest mortality risk ratio among all comorbidities. This risk is increased in the presence of swallowing difficulties. A rehabilitation program is, thus, reasonable for the treatment of these problems.

Design/Methods: A 4-week strength-training program of the expiratory muscles was utilized using a pressure-threshold device. This expiratory muscle strength training (EMST) program was intensive, home-based, and delivered a physiologically challenging load specific to the expiratory muscles and secondarily the suprahyoid muscles. Ten participants with moderate (Hoehn Yahr mean = 2.6; SD = 0.39) IPD were included in this program. Their expiratory muscle strength as well as their swallowing performance were examined before and after exposure to EMST. Expiratory muscle strength was measured using maximum expiratory pressure at the mouth (MEP). Selected temporal and displacement measures of the pharyngeal swallow were used to investigate the participants performance

while swallowing 5 and 10 cc thin liquid boluses. Temporal measures included pharyngeal response time (PRT), hyoid elevation time (HET), hyoid excursion response time (HERT), hyoid excursion time (HEXT), total hyoid movement time (THMT), and closed velopharyngeal time (CVT). The efficiency of each swallow was examined using an 8-point penetration-aspiration scale.

Results: Results indicated over a 50% improvement of MEPs in all patients. Swallowing assessments indicated increased elevation and anterior movement of the hyoid, and decreased temporal measures of PRT, HET, HERT, HEXT, THMT, and CVT after exposure to EMST.

Conclusions: A short, device-driven treatment program specific to the expiratory muscles appears to have a substantial impact on swallow function for patients with IPD. This program can be a part of a rehabilitation program and may have the long-term potential of reducing the risk of aspiration pneumonia.

P247

Telemedicine for delivery of health care in Parkinson's disease

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Objective: To report on the use of telemedicine at the VA Puget Sound Health Care System (VAPSHCS) for follow-up care of patients with Parkinson's disease (PD).

Background: Telemedicine is the delivery of health care or the sharing of medical knowledge over distance using telecommunication technology.

Methods: Patients were located at two Veterans Homes (serving as assisted living facilities and nursing homes), eight medical centers, and one Veterans Center. Most patients would have needed an attendant if they had traveled to VAPSHCS. Each facility had interactive audio-visual equipment, and providers could simultaneously access patients' electronic medical records. A health care provider (physician, nurse, or physician assistant) was present at the patient's side for each visit. Visits lasted 30 to 60 min. For each visit, the movement disorder neurologist rated the degree to which the visit influenced the timely delivery of care and satisfaction in use of this technology. We calculated the costs saved in travel, lodging, and having an attendant accompany the patient.

Results: Thirty-four patients completed 100 follow-up visits. Savings amounted to approximately \$35,000 (transportation, lodging, and attendant travel), 1500 attendant hours, and 60,000 travel miles. For the first 82 telemedicine visits, the video quality was inadequate for scoring all components of the motor Unified Parkinson Disease Rating Scale (UPDRS). For the last 18 visits, the enhanced video quality was adequate for motor UPDRS measurements, except for rigidity. The presence of a primary care physician and nursing staff helped provide first-hand information on patients at the assisted living or skilled nursing facility. The direct interaction between primary care providers and the movement disorder neurologist led to immediate implementation of new recommendations.

Conclusions: Telemedicine can be effectively used for follow-up visits in selected PD patients located at long distances who are unable to travel. It enhances the availability of specialty services and education to remote sites. It saves time and money, and reduces the stress of travel for patients and caregivers. Anecdotally, both patients and providers were satisfied, but further work is needed to confirm and quantify this observation.

P248

Effect of continuous duodenal delivery of levodopa (Duodopa®) on self-reported symptoms in patients with severe Parkinson's disease

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Background: Later stages of Parkinson's disease (PD) are characterised by fluctuations in motor symptoms. In the DIREQT trial, a randomised cross-over trial, various aspects on efficacy of daytime intraduodenal infusion of carbidopa/levodopa (Duodopa®) was studied.

Aim: The aim of this present study was to analyse the effect of Duodopa® on self-reported physical and psychological symptoms.

Methods: Patients were randomised to receive either three weeks of conventional oral therapy followed by three weeks of Duodopa, or *vice versa*. Each day at 8.00, 12.00, 16.00 and 20.00 o'clock every patient was asked with respect to their ability to walk, being OFF, being hyperkinetic, performance of daily chores, muscular cramps, depression and satisfaction with functioning. Electronic diary was used to obtain information. Of 24 patients enrolled 18 completed the trial. Generalized estimating equations (GEE) were employed to analyze differences between the treatments as well as fluctuations over day.

Results: When treated with Duodopa® the patients were more likely to report good ability to walk (OR = 3.4, $P < 0.001$), reduced OFF (OR = 2.8, $P = 0.003$), and being satisfied with functioning (OR = 2.6, $P = 0.01$) compared to conventional oral therapy. Disrespect of treatment major fluctuations were observed over the day. In the morning, patients reported more problems with walking, more OFF-time, and more hyperkinesia than at other hours of the day.

Conclusion: The treatment with Duodopa® had a more positive effect than conventional oral therapy on ability to walk, being OFF and satisfaction with functioning. However, as with conventional oral therapy fluctuations in self-reported symptoms over the day remained with the treatment with Duodopa®. The OFF symptoms in the morning can be explained by the fact that infusion was stopped during the night. The strong variation in self-reported symptoms indicate that trials of treatment effects need to be strictly standardized to avoid biased effect estimates due to variation in timing of measurements.

P249

Reading in Parkinson's disease and Schizophrenia

Z.S. Adwan (Syria)

Objective: To investigate eye movements of patients with Parkinson's disease (PD) and schizophrenia during reading.

Background: In schizophrenia an excessive distractibility has been demonstrated in the antisaccade task.

Design/Methods: Eye movements of 22 PD patients without frontal lobe involvement (HY stages 1 to 4) and 17 schizophrenic patients (by DSM4 criteria with a total PANSS score 31 to 115) were compared to two separate groups of age matched normal subjects during two reading tasks. One task consisted of reading 25 lines of standard reading format (A4 text). The other task was reading the same text lengths (7 lines) of an unusual wide reading card (90°). The text was very simple extracted from a children's story. Eye movements were simultaneously recorded with a high-resolution infrared eye tracker. The reading velocity and number of saccades per line were analysed.

Results: There was no significant difference between reading velocity (mean 3.5°/s, SE 0.4 for A4 and mean 3.3°/s, SE 0.4 for 90° text) or number of saccades (mean per line 12.2, SE 1.08 for A4 and mean 39.3, SE 3.8 for 90° text) of PD patients and reading velocity (mean 3.5°/s, SE 0.2 for A4 and mean 3.3°/s, SE 0.2 for 90° text) and number of saccades (mean per line 13, SE 0.9 for A4 and mean 42.8, SE 3.3 for 90° text) for control subjects. However, schizophrenic patients read much slower (mean 2.6°/s, SE 0.2 for A4 and mean 2.3°/s, SE 0.2 for 90° text) than controls (mean 5.0°/s, SE 0.7 for A4 and mean 6.1°/s, SE 1.8 for 90° text). Schizophrenics made a higher number of saccades (mean per line 17.9, SE 1.1 for A4 and mean 57.5, SE 3.9 for 90° text) compared to controls (mean per line 9.5, SE 0.92 for A4 and mean 36.3, SE 4.0 for 90° text). The higher number of saccades was due to smaller saccades and an increased number of reversed saccades.

Conclusions: While PD patients showed a normal saccadic reading pattern, patients with schizophrenia were reading slower, used a higher number of smaller saccades with an increased number of reverse saccades. The reverse saccades of schizophrenic patients are in agreement with a higher distractibility, which has been attributed to frontal lobe impairment. The increased number and smaller size of saccades is a novel finding. Reading may be an important task for providing a differential diagnosis for frontal lobe dysfunction.

P250

Long-term efficacy of rasagiline in Parkinson's disease

M. Lew, R. Hauser, H. Hurtig, W. Ondo, J. Wojcieszek (Los Angeles, California, USA; Tampa, Florida, USA; Philadelphia, Pennsylvania, USA; Houston, Texas, USA; Indianapolis, Indiana, USA)

Objective: To evaluate the long-term efficacy, safety, and tolerability of rasagiline in the treatment of idiopathic Parkinson's disease (PD).

Background: Rasagiline is a potent, irreversible, selective inhibitor of monoamine-oxidase type B (MAO-B) with no amphetamine-like metabolites. Rasagiline displays neuroprotective activity in vitro and in animal models. Once-daily rasagiline was beneficial as monotherapy in early-stage PD patients during the 6-month placebo phase of a randomized, 12-month double-blind trial¹ (TEMPO, n = 404). Furthermore, patients treated with rasagiline for 12 months had less functional decline, as assessed by total UPDRS scores, than patients whose treatment was delayed for 6 months.²

Methods: An open label extension study of TEMPO was initiated at 32 centers in the United States and Canada in 85% of patients who completed the double-blind trial. All subjects received 1 mg rasagiline once daily and additional dopaminergic treatment as required. Visits were conducted every 3 months. This open label study is still ongoing. The analysis reported herein relates to a cohort of 398 subjects who were treated with rasagiline. At treatment initiation, the mean age of patients was 60.9 (SD 10.8) and their mean disease duration was 1.2 (SD 1.2) years.

Results: Patients have been followed for up to 6.5 years, with a mean time on rasagiline of 3.5 (SD 2.1) years. Out of 306 patients who entered the extension study, 177 patients (58%) continue to be evaluated. Of those patients who reached two years in the study (n = 266), nearly half (46%) were adequately controlled by rasagiline monotherapy. For the entire treatment period (up to 6.5 years) the annual decline rate for patients on rasagiline monotherapy was approximately 2 UPDRS units per year. This compares favorably with reported annual decline rates of 8–14 UPDRS units per year in placebo treated patients.^{1,3–5} In general, rasagiline was safe and well tolerated as monotherapy or with additional dopaminergic therapies.

Conclusions: Long-term treatment with rasagiline is safe, well tolerated, and efficacious for PD patients. Rasagiline monotherapy may offer a new treatment strategy for early stage PD patients.

References

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P251

Early treatment with rasagiline is more beneficial than delayed treatment start in the long-term management of Parkinson's disease

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Objective: To compare the effects of early vs. delayed initiation of rasagiline treatment on the long-term progression of symptoms in patients with idiopathic Parkinson's disease.

Background: Rasagiline is a potent, irreversible, selective inhibitor of monoamine-oxidase type B (MAO-B) with no amphetamine-like metabolites. Rasagiline displays neuroprotective activity in vitro and in animal models. In a double-blind, parallel-group, randomized delayed-start study (TEMPO, n = 404), patients treated with rasagiline for one year had less functional decline, as assessed by total UPDRS scores, than patients whose treatment was delayed for 6 months.¹

Methods: An open label extension study of TEMPO was initiated at 32 centers in the United States and Canada in 306 patients who completed the double-blind portion of this trial. All subjects received 1 mg rasagiline once daily and additional dopaminergic treatment as required. Visits were conducted every 3 months. A cohort of 177 subjects continues to be evaluated in this extension study. These patients have been followed for up to 6.5 years.

Results: At TEMPO start, the mean age of the 177-subject cohort was 60.5 (SD 10.3) and their mean disease duration was 1.1 years (SD 0.7). All 177 subjects have been followed for at least 4.5 years from TEMPO start; their mean time on rasagiline is 5.4 (SD 0.5) years. The advantage of earlier over delayed treatment, previously observed after one year,¹ was maintained over time in this cohort. The mean difference in total UPDRS over time between early and delayed treatment groups was 2.42 (SE 1.04; Repeated Measures Analysis; P = 0.0218).

Conclusion: Subjects who began rasagiline treatment earlier experienced less functional decline, as assessed by total UPDRS scores, than subjects for whom there was a delay of 6 months in treatment start. This observation, previously reported after a 1-year evaluation period, is also valid at long-term follow up. These findings suggest that the clinical benefits of rasagiline are not entirely symptomatic in nature and may reflect a neuroprotective effect.

Reference

1. Arch Neurol 2004;61:561–566.

P252

Effect of L-dopa on neuronal activity of subthalamic nucleus (STN) and substantia nigra (SN) in hemiparkinsonian monkeys

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Objective: To assess the effects of levodopa therapy on the firing rate and firing pattern of subthalamic nucleus (STN) and substantia nigra (SN) in hemiparkinsonian monkeys.

Background: Alteration in functional status of subthalamic nucleus (STN) and substantia nigra (SN) plays a major role in pathophysiology of dopa-induced changes in treatment of Parkinson's disease. Changes in neuronal discharges at these output nuclei may also be responsible for the development of dyskinesia during levodopa therapy. We studied the effect of levodopa therapy on the firing rate and firing pattern of STN and SN neurons in hemiparkinsonian (HP) monkeys.

Methods: Two adult female rhesus monkeys were made hemiparkinsonian by a unilateral intra-carotid injection of 1-methyl 1-4-phenyl, 1-2-3-6-tetrahydropyridine (MPTP). Chronic recording chambers were placed. We recorded single cells in STN and SN in these monkeys after they achieved stable HP state. They were then treated with injectable levodopa (10 mg/kg). Blood dopamine levels were assessed. Single unit recordings were repeated in both those structure while the animals were on levodopa therapy.

Results: We observed a significant decrease in the firing rate in STN and SN after levodopa therapy [Figure 1] (P = 0.027, Fisher Exact test). Firing

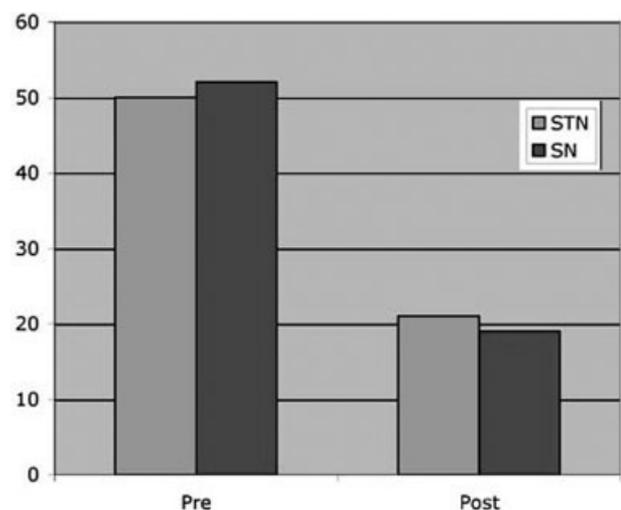


Figure 1. Abstract 252

pattern of the neurons in STN and SN though, remained almost unchanged.

Conclusions: Our findings suggest reduction in output from these two nuclei without any significant normalization of firing pattern. This imbalanced low output from STN and SN may act as preconditioning for development of levodopa-induced dyskinesia.

P253

Detection of motor dysfunction in Parkinson's disease (PD) with timed motor tests (TMT)

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Objective: To investigate which TMT has the highest sensitivity and specificity to detect early parkinsonian motor dysfunction and to discriminate PD from healthy subjects.

Background: Early diagnosis of Parkinson's disease (PD) will become important as neuroprotection will be available. Of the various methods being explored to detect early stages of PD, TMTs could be inexpensive and relatively easily applicable clinical tools. For monitoring of disease severity we developed a battery of TMTs covering main PD motor dysfunctions.

Methods: 17 TMT-subtests were derived from 9 TMT: 1) walking 11 m (sec, n of strides); 2) writing a sentence (sec, cm); 3-5) single- and double-handed pegboard performance (turning and/or displacing 8 pegs, sec); 6,7) finger tapping on 1 key (n of taps/5 sec) and on 2 keys alternatingly (n of taps/10 s); 8) rapid alternating forearm movements (n/5 s); and 9) force of squeezing (kg). Hand function was tested on both sides. Scores of 180 PD patients and 82 healthy, age-matched subjects were analysed using ROC curves. Only observations made in levodopa-naive patients with a disease duration ≤ 5 years were included. Area under the curve (AUC) was calculated for each individual subtest and for combinations of subtests.

Results: By far the best ROC curve was reached for the Pegboard Dexterity Test (i.e., turning pegs upside down (PDT), AUC 0.93). When taking the worst of the two subtests derived from both sides of the body and correcting for hand preference, both for PD and healthy subjects, the AUC improved to 0.95. Even in the first year after symptom onset, the PDT already reached an AUC of 0.92. With a cutoff point at 95% sensitivity, the specificity was 71%. Combinations of PDT and other tests only slightly improved these results.

Conclusions: The PDT is by far the most sensitive TMT in our battery to detect early PD patients, although its specificity with respect to healthy subjects is relatively low for screening programs detecting PD patients among the general population. Therefore, we are investigating combinations with other tests in order to improve specificity so that this easy-to-use and inexpensive PDT can provide not only a useful diagnostic tool in clinical practice but also a screening tool for early PD in a defined population at risk.

P254

Cell death in dopaminergic neurons by MPP⁺ but not dopamine involves DNA damage and PARP

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Objective: To evaluate DNA damage and initiated PARP-ATM-P53 apoptotic pathways in dopaminergic neuron cell death induced by the mitochondrial toxin MPP⁺ and the reactive oxygen species (ROS) inducer dopamine (DA).

Background: Non DA cell systems have been studied for toxin- and radiation-induced DNA strand breakage, which induces poly(ADP-ribosylation) of nuclear proteins predominantly localized adjacent to the DNA strand breaks (DSB), such as PARP. ATM is also rapidly activated by DSB to phosphorylate proteins in chromatin, most notably H2AX histone. PARP also induces the translocation of AIF from mitochondria to the nucleus, which induces nuclear condensation, membrane blebbing, dissipation of the mitochondrial membrane potential, and cell death. Each of these events is caspase-independent. Programmed cell death (PCD) caused by DNA damage has not been studied for the Parkinsonian toxin MPP⁺ or the ROS producer DA in dopaminergic cells.

Methods: Utilizing terminally differentiated SH-SY5Y cells we measured by Western blotting the time course of response to MPP⁺ of Caspases 3 and 9, translocation of AIF from mitochondria to nucleus, and translocation of Cyt C from mitochondria to cytosol. We then tested for cell death in response to MPP⁺ and DA in the presence of specific inhibitors of caspases 1, 3, 6, 7; PARP, p38-MAPK, SAPK/JNK, ROS and an autophagy inhibitor. We also monitored phosphorylated histone H2AX as a marker of DSB after treatment with H₂O₂, MPP⁺, and DA.

Results: Western blotting showed translocation of AIF from mitochondria to nucleus but no changes in caspases or Cyt c. MPP⁺ cell death occurred independently of caspases 1, 3, and 9; JNK/kinase, and ROS inhibitors. MPP⁺ cell death is dependent on calpain and PARP. In contrast DA cell death occurred independently of caspase 1, 3, or 9, and PARP; but is dependent on JNK/kinase and ROS; and is autophagic. Cell death, but not mitochondrial dysfunction, is additive for DA and MPP⁺, which is consistent with their independent pathways. There was a 40% increase of phosphorylated H2AX in response to H₂O₂ and MPP⁺ by 12 h that was reduced by 24 h. There was no consistent increase with concentrations of DA that induce cell death.

Conclusions: We have identified a rapid DNA-damage and PARP dependent PCD to MPP⁺ that is not induced by high concentrations of DA.

P255

Comparison of the metric properties of two specific quality of life measures for Parkinson's disease: PDQ-39 and PDQL (Ecuadorian Versions)

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Objectives: To compare the characteristics of two widely used specific measures for assessment of health-related quality of life (HRQoL) measures in Parkinson's disease (PD).

Background: There is no information comparing metric properties of both measures simultaneously applied to same patients.

Methods: Observational, cross-sectional, one point in time evaluation study. 137 consecutive PD patients were assessed by usual scales (Hoehn and Yahr, UPDRS, Schwab and England), and the Hospital Anxiety and Depression Scale (HADS). HRQoL self-assessment was carried out by means of cross-cultural adapted versions of the PDQ-39 and PDQL.

Distribution of scores, floor and ceiling effect, internal consistency, precision, total scores correlation and multitrait-multimethod analysis were performed.

Results: For both measures, mean and median scores were very close and floor and ceiling effects were satisfactory (0.73%). Skewness was higher for the PDQ-39 (0.61 vs. 0.07). Cronbach's alpha for PDQ-39 dimensions ranged from 0.33 (Social support) to 0.93 (Activities of daily living [ADL]) and for PDQL domains from 0.68 (Systemic symptoms) to 0.85 (Parkinson symptoms). Standard error of measure was 6.3 (Stigma) to 17.6 (Social support) for PDQ-39 and 2.61 (Social functioning) to 3.78 (Parkinson symptoms) for PDQL dimensions. Correlation between both total scores was very high (0.91). Coefficients >0.50 were gained among the PDQ-39 dimensions Mobility, ADL, and Communication and the PDQL domains Parkinson symptoms, Systemic symptoms, and Social functioning. Emotional well-being and Stigma (PDQ-39) correlated significantly with Emotional functioning (PDQL) (-0.67 and -0.64 , respectively). Correlation of Social support and Bodily pain with PDQL dimensions was low ($r < 0.40$). Summary scores of both measures correlated at a similar level with usual PD rating scales and HADS ($r = 0.46-0.76$).

Conclusions: As a whole, PDQ-39 and PDQL have similar psychometric properties, although internal consistency, precision and convergent validity resulted poor for Social support and weak for Bodily pain (both from the PDQ-39). Total scores are almost equivalent.

P256**Autonomic dysfunctions in Parkinson's disease**

J.W. Kim, S. M. Cheon (Busan, Korea)

Background: Symptoms of autonomic dysfunction are frequent and well known in patients with Parkinson's disease (PD). However, these symptoms in PD were relatively ignored compared to prominent dysautonomia in other parkinsonian disorders such as multiple system atrophy. There have been few studies on comprehensive autonomic dysfunction in PD.

Objectives: To know spectrum and frequency (severity) of symptoms of autonomic dysfunctions and to determine correlation between clinical characteristics and autonomic dysfunctions in PD.

Methods: A structured questionnaire about autonomic dysfunctions was administered to 60 patients with PD. Questionnaires were composed of five categories of autonomic functions and recorded with severity or frequency of symptoms: 5 gastrointestinal, 7 urinary, 3 sexual, 3 cardiovascular, and 4 thermoregulatory and sudomotor functions. We took clinical history and characteristics such as disease duration, DOPA dosage, Hoehn and Yahr stage, and activity of daily living (ADL). We also measured Unified Parkinson's disease rating scale (UPDRS) scores in patients with medication "off" state, and analyzed questionnaires to determine correlation between clinical characteristics and autonomic dysfunctions.

Results: All 60 patients (25 male, age 63.73 ± 10.05 year) had at least one type of dysautonomic symptom. Nocturia (71.7%), frequent urination (65.0%), urgent urination (65.0%), anismus (63.3%), excessive salivation (57.7%) were most frequent symptoms. Among 5 categories of autonomic functions, urinary symptoms are also the most common complaints (65%). The severity of gastrointestinal symptoms was correlated with "off" UPDRS scores and clinical characteristics (equivalent DOPA dosage, duration of treatment, ADL) in early patients group. In advanced stage, frequencies of urinary and gastrointestinal symptoms were over 75% and severity of each symptom was well correlated with various clinical parameters. In overall, severity of autonomic dysfunction was correlated with "off" UPDRS scores, ADL, Hoehn and Yahr stage, disease duration, and equivalent DOPA dosage ($r > 0.3$, $P < 0.05$).

Conclusion: Symptoms of autonomic dysfunctions are frequent even in the early stage of PD. We also found that the severity of autonomic dysfunction was correlated with several clinical characteristics.

P257**Blood-brain barrier dysfunction in Parkinson's disease**

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Objective: To demonstrate blood-brain barrier (BBB) dysfunction in Parkinson's disease (PD).

Background: Both genetic and environmental toxic theories have been proposed as explanation for the slowly progressive decline of the catecholaminergic neurons in the midbrain of patients with PD. In vivo in man no cause has been proven to date. Genetic mutations and parkinsonism due to toxins can explain only a small proportion of cases. Here we introduce a new concept which might combine both genetic and toxic components in an explanation of PD causation. A faulty BBB function on the basis of genetic predisposition might in the course of the years allow toxic compounds—or normally in the blood circulating compounds not passing the BBB—to enter the brain in certain regions and damage vulnerable cells like the chemically complex catecholaminergic neurons in the brain stem and maybe others. The P-glycoprotein system is normally present in the BBB in a high concentration. That system serves to remove unwanted substances out of the endothelial cell back into the blood. Recently it has become possible to measure Pgp activity in the brain in man in vivo quantitatively using PET.

Methods: Using PET and the radiotracer [^{11}C]-verapamil, a substrate for the P-glycoprotein, brain uptake was measured in 5 patients with PD [UPDRS-III mean (SD): 20.2 (7.9)] and 5 healthy controls. In each subject, apart from verapamil also cerebral perfusion was measured using radiolabelled water. After data acquisition, volume of distribution images were calculated and normalisation and smoothing steps undertaken. Using SPM

the two groups of subjects were compared and t-constrasts were calculated at a threshold of an uncorrected $P < 0.001$.

Results: The SPM distribution of significant voxels yielded a cluster only in the midbrain region. Brain penetration of [^{11}C]-verapamil was elevated by 18% in the midbrains of the PD patients relative to the healthy controls ($P = 0.02$). All patients showed a higher uptake value compared to any of the controls.

Conclusions: This pilot study demonstrates that the midbrain of PD patients has a defective BBB in respect to the P-glycoprotein molecular efflux pump. This suggests that toxic substances can accumulate more easily in the brain of PD patients than in healthy controls.

P258**Subchronic treatment with rotigotine prevents synaptic degeneration in the MPTP mouse model of Parkinson's disease**

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Objective: To evaluate the neuroprotective property of rotigotine in an in vivo model of Parkinson's disease (PD) using a slow release formulation.

Background: Rotigotine is a novel, non-ergoline, $\text{D}_3, \text{D}_2, \text{D}_1$ dopamine agonist for the treatment of Parkinson's disease (PD). Previously, rotigotine has been shown to be highly active in the MPTP monkey model of PD. So far, it is not known whether rotigotine affects the PD symptoms only or whether it also interferes with the disease progression. Therefore, the present study was initiated to evaluate this potential property of the drug. In order to mimic the constant plasma levels as obtained by administration in patients, a slow release formulation of rotigotine was used which provides constant plasma levels after s.c. administration.

Methods: The slow release suspension was administered at doses of 0.3, 1 and 3 mg/kg. The solution was administered shortly before the MPTP treatment in order to achieve corresponding plasma levels in the post-intoxication period and during the successive six days. To induce neurodegeneration, the mice were treated with MPTP (80 mg/kg i.p. divided in doses of 20 mg/kg and applied every 2 h) and the animals were sacrificed 7 days later. Striatal synaptic density was quantified using radioligand labelling of the dopamine transporter.

Results: During subchronic treatment with rotigotine, the density of the striatal nerve terminals was dose-dependently preserved. Even the lowest dose of 0.3 mg/kg provided significant protection.

Conclusions: Rotigotine dose-dependently prevents the loss of nerve terminals probably due to protection of the neurons after exposure to MPTP. The efficacy of even the lowest dose could be attributed to the continuous dopaminergic stimulation of different dopamine receptor subtypes achieved by the use of the slow release formulation and the prolonged treatment. The results suggest that the neuroprotective potency of the drug could be of additional value in clinical use. However, further experimental (and clinical) studies are needed to confirm this observation.

P259**A double-blind 2-year extension of the Parkinson-CONTROL study comparing fixed doses of piribedil (150 mg/day) and bromocriptine (25 mg/day) in early combination with L-dopa in Parkinson's disease (PD)**

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Objective: This is a double-blind 24-month extension of the 12-month Parkinson-CONTROL study aimed to assess the long term efficacy of piribedil vs bromocriptine, in early combination with L-dopa on motor symptoms of PD patients.

Background: Piribedil is a non-ergot D_2/D_3 agonist with α_2 antagonist properties.

Methods: Among the 425 initially randomized patients, 52 (27 on piribedil and 25 on bromocriptine) were included in the extended administration period, continuing in double blind conditions fixed doses of piribedil (150 mg/day) or bromocriptine (25 mg/day) plus an adjustable L-dopa daily dose. Patients were regularly assessed for safety every 3

months, and underwent to efficacy evaluation (UPDRS III) at month 24 or at withdrawal. Results were analysed on an intention-to-treat basis.

Results: Four patients withdrew from the study before M24 due to adverse events: 3 in the piribedil group (REM Sleep Behaviour disorder, wearing-off and visual hallucinations) and 1 in the bromocriptine group (dizziness due to orthostatic hypotension). 2 patients withdrew for lack of efficacy on bromocriptine, none on piribedil.

A relevant improvement in UPDRS III was maintained versus baseline over 24 months in both piribedil and bromocriptine groups, respectively -7.5 ± 10.0 points and -7.9 ± 9.9 ($P = 0.896$ n.s.).

Interestingly, the L-dopa daily dose adjustment (mg) was significantly lower in the piribedil group than for bromocriptine: respectively from 376 ± 123 vs. 372 ± 138 at baseline to 355 ± 125 vs. 391 ± 157 after 12 months and 382 ± 164 vs. 434 ± 151 after 24 months. At M24 L-dopa daily dose increase (mg) was significantly inferior in the piribedil group: 6 ± 116 vs. 62 ± 76 (E(SE) = 55.5 (27.5), IC95 [0.3–110.7], $P = 0.0486$). Safety profile was good and comparable in the two groups, with prevailing gastrointestinal symptoms.

Conclusions: Early combination of piribedil 150 mg with L-dopa results in relevant improvement of motor symptoms, L-dopa sparing effect and good safety profile in the long-term treatment of Parkinson's disease.

P260

A survey of coenzyme Q10 use in Parkinson's disease clinic outpatients M. Eng, K. Lyons, R. Pahwa (Kansas City, Kansas, USA)

Objective: To conduct a survey to estimate the prevalence and characteristics of coenzyme Q10 use among Parkinson's disease clinic outpatients.

Background: A recent study by Shults et al., reported a trend toward potentially slowing Parkinson's disease progression with the use of higher dose coenzyme Q10. Two other studies have reported a high frequency of complementary and alternative medicine use in Parkinson's disease patients.

Methods: One hundred ninety-seven consecutive new patients to the Parkinson's Disease Clinic at the University of Kansas Medical Center were asked to participate in a coenzyme Q10 survey. All patients were diagnosed with or had an established history of Parkinson's Disease. Patients were asked to indicate if they were using coenzyme Q10, and if so to report any benefits or side effects, amount used and dosing schedule.

Results: Of the 197 patients, only 30 (15.2%) were currently using coenzyme Q10. Unified Parkinson's disease Rating Scale, Hoehn and Yahr, and Schwab and England scores were slightly better in this group. However, all other characteristics were similar, suggesting that the group using coenzyme Q10 were slightly less disabled. Doses and dosing frequency varied from 30–1200 mg/day mean 471 mg/day and from once to four times daily which deviates from that used in the Schults study. Some (26.7%) reported benefit for PD. Only 56.7% of current users consulted their physician about coenzyme Q10. Most patients learned about coenzyme Q10 from non-health care professional resources such as family, friends, and advertisements.

Conclusion: Despite a recent potentially positive study by Schults et al., coenzyme Q10 use was not widespread in this Parkinson's disease outpatient clinic population.

P261

Microelectrode and macroelectrode collision effects during DBS surgery for Parkinson's disease

R.L. Rodriguez, G. Crucian, K.D. Foote, J. Romrell, H.H. Fernandez, M.S. Okun, et al. (Gainesville, Florida, USA)

Objective: To determine the effects of collision on clinical symptoms immediately following both microelectrode recording (MER) and deep brain stimulation (DBS) lead placement for Parkinson's disease (PD).

Background: Improvement is frequently seen in the immediate postoperative period following DBS placement for PD. It is not known if this is a result of a micropallidotomy/subthalamotomy effect that is a consequence of MER, DBS macroelectrode or both.

Design/Methods: 16 consecutive patients undergoing DBS for PD were evaluated intraoperatively with items 20, 21, 22, 23, 24, and 25 from UPDRS Part III plus 2 tests of lower extremity agility graded 0–4. Patients were examined at baseline (immediately before MER), post-MER (after MER, before DBS lead placement) and after collision (before macrostimulation) by an unblinded movement disorders neurologist. Patients were informed of the different stages of the procedure. Data was analyzed by repeated-measures ANOVA with paired comparison post-hoc analyses (with Bonferroni correction).

Results: 14 unilateral and 2 staged bilateral DBS procedures were performed. The average age was 61.2 years. 1 patient underwent Gpi DBS, 9 STN DBS and in 4 patients either STN or Gpi, but remained blinded (ongoing NIH study). The average number of MER passes was 4.56 (range 3–6). There was a significant improvement in total scores between baseline and post-MER (43.3 vs. 39.8; $P = 0.029$), baseline and collision (43.3 vs. 37.3; $P = 0.002$) and post-MER and collision (39.8 vs. 37.3; $P = 0.010$). In individual items scored contralateral to the operated side, there was a significant improvement between baseline and post-MER only for finger taps ($P = 0.029$). Comparing baseline with macroelectrode placement, there were significant changes for UE rigidity ($P = 0.046$), LE rigidity ($P < 0.001$), and dorsiflexion/plantarflexion ($P = 0.034$). There was significant benefit when comparing post-MER and lead collision for LE rigidity ($P < 0.001$).

Conclusions: Both MER and lead collision results in a small benefit in the total scores. Individually, rigidity and bradykinesia revealed the largest changes. The greatest changes occurred between baseline and lead collision. These potential changes must be considered separately from the effects of DBS during macrostimulation.

P262

Spiral analysis: A clinical biomarker for Parkinson's disease

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Objective: To assess upper limb kinematic behavior based on handwritten Archimedean spirals on a computer tablet as a biomarker for early Parkinson's disease.

Background: Studies have assessed clinical biomarkers for PD in an attempt to identify tests with high sensitivity to detect early PD. Our goal is to utilize a combination of a sensitive clinical biomarker as a primary screen and DAT imaging tools as a specific secondary screen to accurately identify early PD patients. In previous studies olfaction testing is utilized to aid in diagnosis of Parkinson's disease with a sensitivity of 86% and a specificity of 53%.¹ Spiral analysis, a test based on handwritten Archimedean spirals acquired on a computer graphics tablet has been validated in healthy subjects, PD, tremor and dystonia patients and may be a useful test to detect early PD.²

Methods: Thirty patients with PD, with suspected PD or at risk for PD underwent spiral testing. All subjects were assessed with UPDRS and were imaged with [¹²³I]β-CIT. To complete the spirals, 10 handwritten spirals from each hand were acquired on a computerized tablet. Data was analyzed using an analysis software program. The founding principle for the spiral quantification is based on "unraveling" the two-dimensional graphic spiral picture into a data series that captures its original kinematic information allowing computational manipulations and clinical correlations. The investigators analyzing the spiral were blinded to all clinical and imaging information.

Results: The mean age was 64 (range: 41–86), UPDRS total in PD patients ($n = 22$) was 35.8 (± 17.22), UPDRS motor was 21.8 (± 11.7). Of the 30 subjects, 22 demonstrated [¹²³I]β-CIT consistent with parkinsonism defined as $<70\%$ of the age expected putamen [¹²³I]β-CIT uptake compared to a healthy database ($n = 99$). Of the 30 patients, spiral analysis was consistent with parkinsonism in 18 subjects, showing a sensitivity of 82%.

Conclusion: These data suggest that spiral analysis may be an easily administered tool to assess early PD. We continue to improve the analysis to optimize specificity and sensitivity in additional studies. Combining

spiral analysis with other tests such as olfaction may provide a more powerful tool in screening and early diagnosis of Parkinson's disease.

References

1. Jennings et al., 2004.
2. Pullman et al.

P263

Continuous subcutaneous apomorphine infusion: An effective and cognitive well-tolerated solution for untreatable motor fluctuations in patients with Parkinson's disease

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Objective: To evaluate in a prospective study, effectiveness and cognitive tolerability of continuous subcutaneous apomorphine infusion (APO) in patients with advanced Parkinson's disease (PD).

Background: Clinical conditions of advanced PD patients are often complicated by motor fluctuations and dyskinesias which may be difficult to control with available oral medications. Deep brain stimulation of subthalamic nucleus (STN-DBS) is a valid therapeutic option but is not accessible for all PD patients.

Methods: 22 consecutive PD patients with medically untreatable fluctuations were assessed for STN-DBS. APO was proposed for both patients waiting for DBS or contraindicated. All patients underwent clinical and neuropsychological evaluation by Unified Parkinson's Disease Rating Scale part III (UPDRS III), Clinical Global Impression (CGI), 24-h ON-OFF diary, Mattis Scale, Stroop Test, Trail Making Test (TMT), Wisconsin Card Sorting Test (WCST) and Verbal Fluency both at baseline and 6 month after APO infusion.

Results: At 6 months, the mean maintenance dose of APO was 56.5 mg/day. This treatment resulted in a significant improvement ($P < 0.05$) of percentage ON (from 34.4% baseline to 49% of time) and significant reduction ($P < 0.05$) of dyskinesias (from 25.7% baseline to 9.9% of time). Mean self evaluation of improvement (CGI) at 6 month was 52% ($P < 0.001$). Mean UPDRS III was reduced by 29.6% (25/108 to 17.5/108). Levodopa doses were reduced by 27%.

The neuropsychological assessment did not change (Mattis Scale) or tended to improve (Stroop Test, TMT, WCST, Verbal Fluency) after APO in comparison with baseline.

Conclusions: APO is an highly effective therapeutic option in management of motor fluctuations in advanced PD patients when either they are waiting for a STN-DBS or DBS is contraindicated. Moreover cognitive status tend to be improved by APO.

P264

Cardiac valve abnormalities in patients with Parkinson's disease

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Objective: The aim of the study was to analyse the frequency of valvular heart disease in parkinsonian patients of a rehabilitation unit for Parkinson's disease (PD).

Background: Restrictive valvular heart disease has been reported in parkinsonian patients treated with pergolide.

Methods: 50 parkinsonian patients (29 men, 21 women, mean age: 64 ± 4 years, HoehnYahr 2–4) were evaluated by echocardiography. A valvular scoring system was used, ranging from 1 (mild) to 3 (severe valvular disease). Current and past treatment with pergolide and ergot derived dopamine agonists was recorded.

Findings: In 31 of 50 patients mild abnormalities of the cardiac valves were found. 13 patients (26%) showed significant restrictive valvular heart disease (score 2–3) including tricuspidal valve regurgitation. Twelve of 13 patients with significant cardiac valve disease had been treated with high dose pergolide in the past. A history of pergolide treatment was present in 30 of 50 patients (61.2%), 1 patient without any cardiac abnormality had received treatment with low dose pergolide in the past. There was no correlation between current treatment with pergolide and valvular heart disease, but there was a close correlation between pergolide treatment in

the past and valvular heart disease ($r = 0.478$; $P < 0.001$), especially between high dose treatment with pergolide and significant valvular heart disease ($r = 0.94$; $P = 0.001$). The correlation between treatment with other ergot-derived dopamine agonists and significant valvular heart disease marginally failed to reach a significant level. Seven patients had never been treated with ergot derived dopamine agonists, none of these patients showed any cardiac valve abnormality.

Conclusions: The rate (62%) of cardiac valve abnormalities in the present study was higher than that reported in the literature. Significant valve disease was present in 26% of the parkinsonian patients. The lack of a correlation between valvular heart disease and current treatment with pergolide was due to a recent change in treatment habits of neurologists. The close correlation between treatment with pergolide in the past and significant valvular heart disease strongly suggests to switch patients taking pergolide to other dopamine agonists, preferable non-ergot dopamine agonists.

P265

Sequence dependent modulation of the simon effect: Impaired inhibitory mechanisms in Parkinson's disease

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This study sought to evaluate automatic response tendencies and inhibitory modulation of automatic processes in Parkinson's disease (PD), utilising a saccadic Simon task with stimulus-response (S-R) compatibility a function of cue shape. The appearance of either a circle or a square in one of two boxes presented peripherally, required the generation of a leftward or rightward horizontal saccade, respectively. Although response times are typically faster when stimulus and response are spatially compatible than when they are not, sequence dependent modulation of this effect results in large differences between S-R compatible and S-R incompatible trials when stimulus and response are spatially compatible in the preceding trial, and reduced or absent differences when stimulus and response are spatially incompatible in the preceding trial. Unlike control subjects, PD patients demonstrated significantly shorter saccadic latencies overall, compared to a baseline condition involving endogenously-driven saccades, and demonstrated a Simon effect (relatively faster response for S-R compatible trials), irrespective of the preceding trial. This suggests impaired modulation of the Simon effect in PD, consistent with Praamstra and Plat's (2001) proposal of disinhibition, or failed suppression, of direct, stimulus-driven visuomotor activation. Significantly, patients also generated more erroneous response to cue stimuli than control subjects. These results demonstrate the pivotal role of the basal ganglia in the regulation of context-dependent neural activity.

P266

Direct and indirect costs in Parkinson's disease

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Objective: Processing and analysis of the direct and indirect (economic) costs in the treatment of patients with Parkinson's disease (PD).

Background: Data regarding the direct and indirect costs incurred in the treatment of PD have been incomplete so far. Particularly, the indirect costs are hardly being considered, although they do have a substantial bearing on the national economy.

Methods: This study prospectively ascertained all costs incurred over a period of 3 years in 117 PD patients, i.e., costs for medication, medical therapies, diagnostic procedures, hospitalizations, remedies, and aids. Moreover, it included costs related to decreased earning capacity, housing modifications, home care, early retirement, transportation costs, etc.

The fee schedules applicable within the German Health Care system (GOÄ, EBM) were used to evaluate the individual items; drugs were rated according to their selling price in pharmacies; remedies and aids according to the reimbursements granted by costing units.

The nursing rates legally provided for, flat mileage rates, and information gathered from patients and manufacturers were, among others, incorporated to assess the indirect costs.

Results: We studied a total of 117 patients (78 male). Their mean age was 67.5 years, the majority of them graded in the HY stages 2 and 3.

Results: The average total costs per patient and month amounted to 606.29€ Breaking them down, pharmaceuticals run up to 495.15€, remedies to 51.43€, aids to 11.08€, therapies to 13.01€, extraordinary diagnostic workup (MRT, SPECT, PET) to 20.05€, and hospitalizations to 15.57€. The total of average indirect costs per month and patient amounted to 342.80€. These are made up by 121.98€ due to the disability to earn a livelihood (including early retirement), 76.91€ for nursing/home care, 24.97€ for transportation, 107.84€ for housing modifications and 11.10€ for ancillary expenses.

Conclusion: The costs for pharmaceuticals are the biggest item among the direct costs (495.15€ = 81,67%), whereas disability to earn a livelihood, including early retirement, constituted the biggest factor among the indirect costs (35.58% = 121.98€). The nursing costs of 24.97€ referring to outpatients alone, are explained by the great number of subjects still in the early stage of disease.

P267

The cost-effectiveness of continuous duodenal delivery of levodopa (Duodopa®) in patients with severe Parkinson's disease

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Objective: To explore costs and health benefits of replacing conventional oral therapy with Duodopa® for severe Parkinson's disease (PD).

Background: Later stages of (PD) are characterised by fluctuations in motor symptoms. Intraduodenal infusion of levodopa (Duodopa) allows more stable plasma levels and better motor symptom control.

Methods: In the DIREQT trial, 24 patients aged 50–79 years with Hoehn Yahr stage 2.5–4.0 (at best) were randomised to receive either 3 weeks of conventional oral therapy followed by 3 weeks of Duodopa, or *vice versa*. Later, patients could choose to switch permanently to Duodopa. Health Related Quality of Life (HRQOL) was recorded with the 15D instrument at entry into the trial, during the trial, and then at 8 follow-ups during the subsequent 6 months. Use of health care was registered before, during and after the trial. Two-year costs and health consequences of Duodopa and conventional therapy were estimated in a decision analytic model. Utilization of care was based on trial data and published studies. Unit costs were based on market prices and customary charges in Sweden.

Results: The mean 15D-scores were 0.77 for Duodopa and 0.72 for conventional therapy with considerable variation in scores for individual patients over time. The expected two year cost was \$93,600 for Duodopa and \$28,700 for conventional therapy. The expected number of QALYs was 1.48 and 1.42, respectively, representing a ratio of \$1.02 mill. Per QALY (all values discounted at 3%). This ratio was most sensitive to uncertainty in drug prices, discount factor and the cost of neurologist visits.

Conclusions: The cost per QALY for Duodopa therapy is higher than conventional cost-effectiveness thresholds. The results, however, should be interpreted cautiously due to large intra-individual variability in HRQOL. The societal valuation of Duodopa will depend on its costs and benefits, the severity of PD, the implications of Duodopa's orphan drug status and the cost-effectiveness of competing therapies (apomorphine infusion and deep brain stimulation).

P268

Non-linearity of Parkinson's clinical progression: Implications for sample size calculations in clinical trials

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Objective: To provide a method to estimate the change in Total UPDRS score, and its associated variance, in order to construct sample size calculations for a long-term neuroprotection trial.

Background: Estimation of sample size for long-term studies of neuroprotection in PD requires information on expected clinical decline. These values may be obtained by analyzing existing long-term data sets or by prediction models of clinical decline applied to available data from shorter-term trials. The most commonly used measure to track clinical decline is the Unified Parkinson's Disease Rating Scale (UPDRS) but this measure is also affected by symptomatic therapy. Models can help to better understand this behavior of the UPDRS after initiation of symptomatic therapy when scores will improve and eventually start deteriorating again.

Methods: We developed a non-linear model of UPDRS progression after introduction of symptomatic therapy. The model is specified as a non-linear mixed effects model and is applied to three different data sets from clinical trials. The model is then used to produce estimates for the change in UPDRS and its associated variance for a period of up to 5 years of follow-up. The estimates produced by the model serve as the basis for sample-size calculations for different lengths of follow-up (1–5 years) and for different values of clinically meaningful change in UPDRS.

Results: We find that despite differences in the short-term benefit of the dopaminergic drugs, after a period of approximately six months UPDRS scores progress linearly at an estimated rate of approximately three points a year. The sample size that is required for a clinical trial where the baseline coincides with initiation of symptomatic therapy is very large. On the other hand, if baseline is set at 6 months after initiation of symptomatic therapy then the sample size required will tend to decrease with length of follow-up.

Conclusions: Sample size calculations based on these estimates indicate a substantial reduction in sample size if patients are required to be on symptomatic treatment for a period of time before randomized to a neuroprotective trial.

P269

A nationwide survey of excessive daytime sleepiness in Parkinson's disease in France: "PARKIN-SOM"

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Objective: To determine the frequency and severity of excessive daytime sleepiness (EDS) and "sleep attacks" (SA) in a large cohort of ambulatory outpatients with Parkinson's disease (PD) in France.

Background: Much concern has been put forward regarding EDS and SA in PD and the risk of traffic accidents (TA). However, large epidemiological surveys with face to face interviews on this topic are scarce. The Epworth Sleepiness Scale (ESS) has proved adequate sensitivity and specificity for predicting episodes of falling asleep while driving.

Methods: Between January 1st and September 30th 2004, a national representative sample of 400 neurologists was asked to enroll 10 consecutive non-demented PD patients. After informed signed consent, patients were asked to fulfill the ESS. Demographic data, disease duration and severity, co-morbidities, daily medications, and history of TA were collected by face-to-face interview.

Results: A total of 2037 PD patients completed the study. Mean age was 69.8 ± 9 years, mean disease duration = 6.2 ± 4.7 years, mean disease severity = 2.2 ± 0.9 (Hoehn Yahr), and = 81.2 ± 13.3% (Schwab and England). Of the total population, 50.4% were active drivers, of whom 2.7% experienced TA in the past year. Mean ESS score of the total population was 7.2 ± 4.8 of whom 28.6% scored >9 suggestive of EDS; 27.3% of the drivers also scored >9 as well as 29.6% of those with previous TA. The mean ESS score of drivers was significantly lower than non-drivers (6.9 ± 4.6 vs. 7.4 ± 5, $P < 0.05$), but the mean ESS score of drivers with TA was higher than in drivers without TA (8.1 ± 5.4 vs. 6.9 ± 4.6) although not reaching significance. The chance of dozing while driving was slight for 11.8%, moderate for 3.2% and high for 1.1%. The chance of SA while driving was slight for 9.9%, moderate for 0.9% and high for 0.7%. The mean ESS score was not significantly different whether the patients took levodopa alone (n = 458), dopamine agonists alone (n = 201), both (n = 606), or other combinations (n = 558): 6.8, 6.7, 7.5 and 7.4, respectively.

Conclusions: We here demonstrate that more than one fourth of ambulatory PD outpatients report EDS (ESS score >9) whether they drive or

not. A chance (slight to high) of dozing while driving was reported by 16% and that of SA by 11.5% of drivers.

P270

Safety of rasagiline in elderly Parkinson's disease (PD) patients

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Objective: To determine if the overall good safety profile for rasagiline, a relatively selective and irreversible monoamine oxidase type-B inhibitor, applies also to elderly patients with PD.

Background: The safety of anti-PD treatments in the elderly has not been reported, but is clinically important because of our increasingly aged population. Rasagiline has been examined as monotherapy (TEMPO, Arch Neurol 2002;59:1937-1943) and in combination with levodopa (PRESTO, Ann Neurol 2003;54:S27) in two 6-month randomized placebo-controlled clinical trials and found overall to be safe and well tolerated.

Methods: Safety data (total adverse effects, total serious adverse effects, dyskinesias, hallucinations, confusion, and symptomatic orthostatic hypotension) were examined in the TEMPO (N = 404) and PRESTO (N = 472) studies comparing (chi-square or Fisher's exact tests as appropriate) the placebo and rasagiline-treated groups among younger (<70 years) and older (≥ 70 years) subjects.

Results: In both studies, total adverse effects, total serious adverse effects, and symptomatic orthostatic hypotension were not significantly (all $P > 0.05$) affected by treatment (rasagiline or placebo) or age (younger or older). Hallucinations were infrequent and did not occur more commonly among elderly patients who were administered rasagiline alone. However, hallucinations were reported more frequently ($P = 0.0130$ for 4-way comparison) among elderly patients receiving rasagiline in combination with levodopa (12% for elderly vs. 2% for younger, $P = 0.0034$) compared with their placebo counterparts (4% vs. 3%). Although rasagiline was more frequently associated with dyskinesia than placebo when given in combination with levodopa (18% vs. 10%, $P = 0.0254$), there were no age-related differences (19% and 18%, $P = 0.77$). Confusion was infrequent (0-4%) in both studies and unrelated to treatment assignment or age.

Conclusions: Rasagiline was generally safe and well tolerated in PD patients regardless of age or concomitant levodopa treatment. However, the infrequent but increased occurrence of hallucinations in elderly PD patients treated with rasagiline in combination with levodopa prompts heightened clinical surveillance in this population. Such precautions may also apply to other dopaminergic drugs administered to elderly PD patients.

P271

The efficacy of visual cues to treat patients with Parkinson's disease experiencing freezing of gait (FOG) episodes: A pilot study

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Objective: To examine the effects of visual cueing on freezing of gait (FOG) in patients with Parkinson's disease (PD).

Background: Approximately 60% of patients with PD experience FOG. FOG is a poorly understood clinical sign of PD and interferes with quality of life and contributes to falls. In the clinical setting it has been observed that external visual cueing improves motor performance by facilitating the interruption of FOG.

Methods: Twenty-two subjects with PD who experienced FOG were consented to participate in a crossover intervention trial. Subjects were randomized to a visual cue intervention, provided by a laser lightbeam affixed to a rolling walker, or to a rolling walker without laser lightbeam. All subjects performed three walking tasks that induced FOG during turning/negotiating obstacles, starting and approaching a terminal object. Performance measures recorded during the walking tasks included (1) the time to complete the task, (2) the number of steps taken to complete the task, and (3) the number of freezing episodes that occurred during the task.

Results: The mean age was 75.18 years (SD 7.65) and the mean disease duration was 14.27 years. Subjects who were assigned to the light beam

intervention demonstrated significantly less FOG during the walking task that required repeated stopping and starting ($P = 0.007$) and FOG frequency was decreased (approaching significance $P = 0.062$) during the walking task of moving toward a terminal object. During the crossover trial, subjects assigned to the light beam demonstrated more FOG (approaching statistical significance $P = 0.067$) during the walking task that required repeating stopping and restarting.

Conclusions: Our data suggest patients with PD and FOG that utilize visual cues with a rolling walker to break FOG episodes is inconclusive. Fatigue may influence the ability of external visual cues to break FOG episodes. Limitations include small sample size.

P272

The effectiveness of bilateral DBS STN in advanced Parkinson's disease

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Objective: To estimate the effectiveness of the bilateral deep brain stimulation of subthalamic nucleus (DBS STN) in advanced Parkinson's disease (PD).

Material and Methods: Since 2003 we have used the bilateral DBS STN at 11 patients. Middle age of patients was 54 ± 9 years; the anamnesis of Parkinson's disease was 9 ± 4 years. All patients had 3-5 stages by Hoehn Yahr scale. The results of treatment were estimated on UPDRS and Schwab England Scale (SchE). The quality of life was examined on PDQ-39. All cases were surveyed in OFF-med, and in the best medication condition (ON-med). Patients were examined before surgery and every 6 months after surgery. Results of DBS STN were compared with preoperative findings. We used Luria's method for the neuropsychological examination. Surgical outcomes were as follows: unfavorable results (poor UPDRS at OFF-med or improved UPDRS at OFF-med combined with deterioration at ON-med stage, as well as deterioration evaluated by SchE and PDQ-39); satisfactory results (<33% improvement by UPDRS at OFF-med., no deterioration at ON-med. And improvement by SchE and PDQ-39); good results (>33% improvement by UPDRS at OFF-med combined with improvement SchE, PDQ-39 and L-dopa reduction); excellent results (>50% improvement at OFF-med and SchE, HY, PDQ-39 improvement when L-dopa was completely or nearly stopped).

Results: Postoperative MRI confirmed correct electrode position at all cases. We have received: 1 unfavorable result, 3 satisfactory, 5 good and 2 excellent. A 70-year-old patient with unfavorable result had severe vegetative disorders (perspiration, urination, swallowing dysfunction, etc.) and the depression. Three cases with satisfactory results were observed in patients with vestibular schwannoma, L-dopa-resistant tremor and cognitive disorders. So, all patients with unfavorable and satisfactory results had L-dopa-negative symptoms before surgery.

Conclusions: DBS STN is considered to be an effective method for treating advanced Parkinson's disease (PD). However, improvement in quality of life was not observed in all patients with best effect of treatment by L-dopa before surgery. Probably, presence of L-dopa-negative symptoms doesn't allow expecting good rehabilitation effect in PD-patients.

P273

Validation of a self-reported swallowing disturbances questionnaire (SDQ) in patients with Parkinson's disease

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Objective: To develop and validate a self-reported swallowing disturbances questionnaire (SDQ) in patients with Parkinson's disease (PD) by an objective assessment with fiberoptic endoscopic evaluation of swallowing (FEES) findings.

Background: Swallowing disorders are well recognized, but often underestimated in people with PD. Asymptomatic patients may miss swallowing evaluation and therapy thus be placed at risk. A self-reported questionnaire on swallowing difficulties can detect PD patients with early symptoms and increase the awareness of the medical community.

Method: Fifteen PD patients (10 men) from the Movement Disorders Unit with complaints of swallowing disturbances were included in the

study. Mean age was 64.3 years (63–84), with PD duration of 6.8 years (0.5–15), and mean average HY stages of 3.2 (1–5). Each patient completed a self-reported questionnaire comprising 10 questions of swallowing disturbances. Four questions related to the oral phase of swallowing and 6 questions related to the pharyngeal phase. All patients underwent a FEES exam by an otolaryngologist and a speech language pathologist. The questionnaire and the FEES results were divided according to the oral and pharyngeal stages of swallowing.

A total score was given to the patient's swallowing status by Dysphagia Objective Severity Scale (DOSS). Statistical analysis was performed using alpha Cronbach, Spearman's correlation and Mann-Whitney non-parametric test. Significant was considered $P < 0.05$.

Results: A significant correlation was observed between SDQ and FEES results (oral phase $P = 0.02$, pharyngeal phase $P = 0.07$). The DOSS score and the questions related to the oral and pharyngeal phases were correlated respectively ($P = 0.03$, $P = 0.29$).

Alpha Cronbach demonstrated internal consistency for the questions in the questionnaire ($\alpha = 0.85$).

Conclusion: This study demonstrates that the self-reported questionnaire on swallowing difficulties can help to detect symptoms of dysphagia and provide useful information on clinical abnormalities of swallowing in patients with PD. According to our results, patient's report in the questionnaire was correlated with FEES results when evaluating oral and pharyngeal stages of swallowing.

P274

Entacapone, a COMT inhibitor, increases the long-duration response (LDR) to L-dopa in unilateral 6-hydroxydopamine-lesioned rats

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Objective: To investigate whether the administration of entacapone, a catechol-O-methyl-transferase (COMT) inhibitor, modifies the long-duration response (LDR) to L-dopa in an experimental model of parkinsonism.

Background: The LDR to L-dopa is a component of the therapeutic response in Parkinson's disease (PD). LDR is a sustained antiparkinsonian benefit that lasts many hours or days after discontinuation of treatment. It has been reported that the LDR reflects postsynaptic pharmacodynamic changes that could be modified by various types of stimulation suggesting that chronic exposure to continuous dopaminergic stimulation may change the length of the LDR. Agents that inhibit COMT metabolism of L-dopa enhance its brain availability providing a more continuous dopamine-mediated stimulation. The effect of COMT inhibitors on LDR is still unknown.

Methods: Male Sprague-Dawley rats were unilaterally lesioned with 6-OHDA in the medial forebrain bundle. Rats were treated with L-dopa (25 mg/kg, twice daily, $n = 9$), L-dopa + entacapone (30 mg/kg, i.p., twice daily; $n = 8$) or saline ($n = 5$) for 22 days. Rotational behavior was weekly measured. To assess forelimb akinesia the cylinder test was used after the administration of a test dose of L-dopa (6 mg/kg). Forelimb akinesia was weekly evaluated and 4 h, 2, 5, and 7 days after L-dopa withdrawal.

Results: 6-OHDA lesion induced a deficit in the use of forelimb contralateral to the lesion ($P < 0.01$). Treatment with L-dopa improved the performance of the impaired limb ($P < 0.01$). This improvement persisted until 2 days after L-dopa treatment withdrawal. Animals that received L-dopa + entacapone showed a persistence of the improvement until 5 days after L-dopa withdrawal. As expected, the duration of the rotational response to L-dopa significantly decreased 23% by the 22nd day of treatment ($P < 0.01$). This motor fluctuation was not observed in the animals treated with L-dopa + entacapone.

Conclusion: Early coadministration of entacapone with L-dopa was associated with an increase in the length of the LDR and an attenuation of the short-duration response to L-dopa. These findings support the hypothesis that the treatment of L-dopa with a COMT inhibitor induces a long-duration clinical benefit when combined from the initiation of therapy in patients with PD.

P275

Long- and short-duration response to L-dopa in the experimental model of parkinsonism in rats with an unilateral nigrostriatal lesion

C. Marin, E. Aguilar, J.A. Obeso (Barcelona, Spain; Pamplona, Spain)

Objective: To investigate the concomitant presence of the short-duration response (SDR) and the long-duration response (LDR) to L-dopa in an experimental model of parkinsonism.

Background: The therapeutic response to L-dopa in Parkinson's disease (PD) consists of two components: the SDR, which is an improvement in motor disability that lasts a few hours after the administration of L-dopa, and the LDR, which is a sustained antiparkinsonian benefit that lasts several days after discontinuation of treatment. Understanding the basis of the LDR might offer many therapeutic benefits in PD, however, the LDR has not been investigated in experimental models.

Methods: Male Sprague-Dawley rats were unilaterally lesioned with 6-OHDA (8 μ g) in the medial forebrain bundle. Rats were treated daily with L-dopa (25 mg/kg, twice daily, $n = 9$) or saline ($n = 8$) for 22 days. Rotational behavior was weekly measured. To assess forelimb akinesia the cylinder test was used and the number of supporting well contacts that were carried out with each of the right (parkinsonian) and left forelimb was counted after 45 min of the administration of a test dose of levodopa (6 mg/kg). Forelimb akinesia was weekly evaluated and 4 h, 2, 5 and 7 days after L-dopa withdrawal.

Results: 6-OHDA lesion induced a significant deficit in the use of forelimb contralateral to the lesion ($P < 0.01$). Treatment with L-dopa improved the performance of the impaired limb after the test dose of L-dopa being significant after 3 days of treatment ($P < 0.01$). Upon withdrawal of L-dopa, the motor benefit persisted for 2 days reaching baseline values after 5 days without treatment. In 6-OHDA-lesioned rats that received control injections of saline, the degree of limb use asymmetry did not show any spontaneous amelioration. As expected, the duration of the rotational response to L-dopa significantly decreased 23% by the 22nd day of treatment (136 ± 8 min on day 1 to 106 ± 7 min on day 22, $P < 0.01$).

Conclusion: Treatment with L-dopa for 22 days in rats with a unilateral lesion of the nigrostriatal pathway induces two kinds of responses, the SDR and the LDR. In this experimental model, motor fluctuation in L-dopa-induced rotational behavior is related to the SDR, whereas the improvement in forelimb akinesia might be related to the LDR.

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Application of systems performance theory to the UPDRS: Preliminary exploration

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Objective: To investigate UPDRS revision in light of performance theory concepts.

Background: A MDS Task Force recently reviewed the UPDRS and recommended development of a new version that capitalizes on its strengths and rectifies its weaknesses. Developments in General Systems Performance Theory (GSPT) and human performance measurement applications¹ provide another perspective relevant to UPDRS revision. GSPT requires performance measures be defined using a resource construct (representing desirable quantities in contrast to impairments) and provides a framework to address the complex, multidimensional and hierarchical nature of human performance. Whereas the UPDRS uses addition to combine elements of impairment, GSPT suggests use of multiplication to compute the volume of a "multi-dimensional envelope." This volume represents an individual's capacity to perform tasks that draw on the constituent performance resources.

Methods: Subjects with Parkinsonism ($n = 114$) were evaluated in practically defined "off" and "on" (~1 h after medication) states. Selected UPDRS Subscale III items (rapid alternating movements and leg agility) were used to compute subscores by addition and also transformed to represent performance resource measures that were combined using mul-

tiplication. Individual and two and four limb composite measures for “off” and “on” states were used to compute “percent change” in performance.

Results: “Percent change” values ranged as follows: 1) individual measures (14.6–18.1), 2) addition-based composites (15.2–17.2), and 3) multiplication-based composites (30.8–63.7, with percent change increasing with the number of individual measures included).

Conclusions: UPDRS impairment items were amenable to transformation to performance resource/capacity format. Multiplicative composites were more sensitive, conceptually-based, and reflect the interaction of different performance resources that occurs in the execution of daily activities. GSPT offers new and relevant insights into UPDRS revision and expansion of this pilot effort is warranted.

Reference

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P277

Addressing non-motor impairments in Parkinson’s disease: The new version of the UPDRS

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Objective: To assess the prioritization of non-motor impairments in the new *Movement Disorder Society (MDS)*-sponsored version of the UPDRS.

Background: The MDS organized a Task Force critique of the UPDRS¹ that recommended developing a new version with clearer guidelines, more specific anchors, more attention to non-motor aspects of PD, and the introduction of rating options to capture very mild impairments.

Methods: The MDS president appointed a director who organized a committee of 22 additional members. Using the MDS critique, members adapted the original UPDRS but retained 0–4 anchors for all items. Whereas non-motor aspects of PD had been assessed in different portions of the original scale (Parts 1 and 4), strategies were discussed to consolidate non-motor disabilities into one section. Drafts of revised Parts I–IV were developed by individual sub-committees and then circulated to the entire group for review. A 1-day meeting finalized wording and resolved debated issues before formal presentation to the MDS membership. A clinimetric testing program was also designed.

Results: The new version of the UPDRS has four sections: Non-motor experiences of daily living, Motor experiences of daily living, Motor examination, and Motor complications. Whereas non-motor items were spread throughout the original scale, they are confined to Part I in the new version with 11 items. New items of focus are anxious mood, sleep quality at night, ability to stay awake, urinary function, and constipation. All rating options throughout the scale are anchored with in parallel with 0 = normal; 1 = slight; 2 = mild, 3 = moderate, 4 = severe. An appendix accompanies the UPDRS to direct raters to complementary scales that focus on more detailed analysis of individual areas of impairment or disability.

Conclusions: The new version of the UPDRS clearly divides non-motor and motor elements of PD to allow separate ratings as well as a Total UPDRS score. Analytic methods for treatment evaluations may vary depending on the hypothesis tested and the anticipated impact of a treatment on motor vs. non-motor aspects of PD.

Reference

1. *Mov Disord* 2003;18:738–750.

P278

Binge eating behavior in Parkinson’s disease patients on dopamine agonist therapy

M.J. Nirenberg, C. Waters (New York, New York, USA)

Objective: To report several cases of binge eating behavior in Parkinson’s disease (PD) patients on dopamine agonist therapy.

Background: Recently, dopamine agonists have been associated with compulsive gambling and other repetitive, purposeless behaviors (“punding”). We identified several PD patients with binge eating, a compulsive behavior that has not been previously reported in this patient population.

Methods: We interviewed and reviewed the charts of several PD patients who developed new-onset binge eating during the course of their illness.

Results: Each of the identified patients reported compulsive eating behavior. This usually occurred in binges, often in the middle of the night. In all cases, this behavior resulted in significant, undesired weight gain. In some patients there were other new-onset repetitive behaviors such as compulsive gambling. Each of the affected patients was taking a dopamine agonist medication when the binge eating occurred, sometimes at higher than recommended doses.

Conclusions: Physicians should be aware that binge eating resulting in significant weight gain may occur in PD, possibly as a side-effect of dopamine agonist medications. Given the known risks of the associated weight gain and obesity, further investigation is warranted.

P279

The cost-effectiveness of screening for pre-symptomatic Parkinson’s disease depends on the availability of neuroprotective therapies

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Objective: To determine the cost-effectiveness of various screening strategies for pre-symptomatic Parkinson’s disease.

Background: Recent research has identified approaches, such as olfactory testing and imaging of the pre-synaptic nigro-striatal system, to identify individuals at high risk for developing Parkinson’s disease (PD). In the presence of effective neuroprotective therapies, identification of at-risk individuals would permit the targeted use of neuroprotective agents to delay or prevent the emergence of symptomatic PD.

Methods: We used decision-analytic modeling to estimate the incremental cost-effectiveness of several screening strategies including the following: olfactory testing alone, dopamine transporter imaging alone, and a combination of olfactory testing followed by dopamine transporter imaging to detect pre-symptomatic PD in at-risk individuals. We derived estimates of the incidence of PD, sensitivity, and specificity of diagnostic tests, and costs and potential benefits of therapy from the available literature. Potential benefits were measured using quality-adjusted life-years (QALYs). Sensitivity analyses were performed on model parameters, including disease incidence, test characteristics, and cost and benefits of therapy.

Results: Screening for pre-symptomatic PD was not cost-effective in the absence of neuroprotective therapies. However, under assumptions of modest neuroprotective effects which allowed the addition of one QALY over a 10-year disease course, the incremental cost-effectiveness of the screening strategy that used olfactory testing followed by dopamine transporter imaging was \$30,000 per QALY. The two other screening strategies as well as a “treat all” strategy were dominated by the screening strategy of olfactory testing followed by imaging. The model was sensitive to the underlying incidence of PD, characteristics of the olfactory and imaging tests, the costs and benefits of therapy, and the reassurance value of a negative test.

Conclusion: Screening for pre-symptomatic PD in asymptomatic at-risk individuals could be cost-effective in the setting of relatively modest neuroprotective effects. The results provide economic support for the development of preventive therapies for PD.

P280**Pain and Parkinson's disease**

M. Kapisiyi, J. Kruja (Tirana, Albania)

Objective: Pain is reported to be a common complaint of Parkinson's disease (PD) patients. The objective of our study is to evaluate the incidence and characteristics of pain in PD patients

Setting of the study: Movement Disorders Center, University Hospital Center "Mother Theresa."

Method: We investigated 62 PD patients (4 females, 28 males), who were following up at our Movement Disorders Center, for at least 1 year. They were asked if they have experienced any kind of pain during the course of their disease. Those who responded positive passed an interview about pain characteristics (localization, quality, intensity, duration, medication use to treat PD and medication use to solve the pain). Further examination (when needed) was performed to exclude other causes of pain than PD. The stage of disease was evaluated according Modified Hoehn and Yahr Scale and the presence of motor complications was evaluated according UPDRS score.

Results: 47 patients (76%) reported to experience pain. Rheumatic disease was found to be the cause of the pain in 5 patients (8%). One patient was found to suffer lumbar disc herniation. Pain was attributed to PD in all other cases (41 patients). The mean Hoehn and Yahr stage was 2.5 (1-4).

There were no differences in age of onset, sex, duration of disease and Hoehn and Yahr stage between patients with and without pain. 23 patients (56%) with pain experienced wearing off phenomenon, comparing to 4 patients (27%) without pain. Dyskinesias were present in 18 patients (44%) in the pain group comparing with only 2 patients in the other group. One patient reported pain to be the first sign of his PD. In 32 patients medication used to treat PD solved the pain. Pain was reported to be "moderate" from 80% of patients. The most common location of pain in our patient was shoulder and back (24 patients). Neck and leg were also affected by pain.

Conclusion: Pain is a common complaint of PD patients. It is with moderate intensity; more present in patients with levodopa induced complication, especially dyskinesias Treatment of PD improve the pain.

P281**Clinical and gene analysis of early onset Parkinson's disease in Korean patients**

E.J. Chung, W.Y. Lee, W.T. Yoon, C. S. Ki (Seoul, Korea)

Objective: To investigate the clinical characteristics of early onset Parkinson's disease (EOPD) and analyze the various types of gene mutation in *parkin* gene in Korean patients.

Background: EOPD, defined as PD beginning before the age of 50, is clinically and genetically heterogeneous. However, systemic analysis of clinical features and gene mutation has not been performed in Korea.

Methods: We enrolled 58 patients (2.9%; 38 men and 20 women) with EOPD out of 2000 patients with PD, who was diagnosed by NINDS diagnostic criteria. We analyzed the clinical features including initial symptoms, Hoehn and Yahr (H-Y) stage, levodopa responsiveness, dystonia, presence of levodopa-induced dyskinesia, dysautonomia, and dementia. We performed a dosage analysis for 9 of 12 exons on *parkin* gene.

Results: The duration of disease was 27.8 ± 21.6 (mean \pm SD) months. The initial H-Y stage was 1.9 ± 0.5 . Tremor at rest was the most frequent initial symptom (48%) followed by bradykinesia (38%), gait disturbance (24%), and dystonia (7%). Although dystonia as an initial symptom was not frequent, dystonia developed in 21 patients (36%). As the onset of parkinsonism was earlier, dystonia was more frequently detected ($P = 0.0019$). Minimal status examination (MMSE) was performed in 19 patients and 4 patients had MMSE score below 16 percentile. All of the EOPD patients showed good response to levodopa. Minimum effective dose of levodopa was 344 ± 210 mg/day. Fifteen of 45 EOPD patients (33%) suffered levodopa-induced dyskinesia after 17.2 ± 19.9 months of levodopa therapy. Dysautonomia was shown in 25 patients (43%). Heterozygous deletions in exon 2, 3, and/or 7 were found in 3 patients (5.2%).

Conclusions: In accordance with other studies, dystonia was frequently accompanied with parkinsonism in EOPD. Early onset of disease tends to have more frequent dystonia. However, in our study, tremor at rest or gait disturbance as an initial symptom was higher than those of previous studies. Our study suggests that levodopa-induced dyskinesia, dysautonomia, and mild cognitive impairment can be presented in the early stage of EOPD. We detected the *parkin* mutation with heterozygous deletion of exon 2, 3, and/or 7 in Korean patients with EOPD.

P282**Valvular heart disease associated with low cumulative dose of pergolide in the patient with Parkinson's disease**

E.J. Chung, W.Y. Lee (Seoul, Korea)

Objectives: To report the clinical features, echocardiographic and histopathological findings of valvular heart disease (VHD) associated relatively low cumulative dose of pergolide in the patient with Parkinson's disease (PD).

Background: Pergolide-associated VHD (PAVHD) has been recently reported. According to the literature, a relatively high dose of pergolide can cause VHD involving mitral and tricuspid valve. We experienced a patient with PAVHD who was treated with low daily dose and low cumulative dose of pergolide.

Case: A 61-year-old man with PD presented with 1-week history of severe dyspnea and lower limb edema and was admitted to our thoracic surgery department under the diagnosis of heart failure. He had been administered with pergolide combined with levodopa since 1995. For 9 years, pergolide was slowly titrated from 0.1 mg up to 2.25 mg per day. The cumulative dose of pergolide was approximately 2730 mg. Transthoracic echocardiography showed the rupture of chordae tendinae and multivalvular dysfunction such as severe mitral, moderate tricuspid, and mild aortic regurgitation. Under the parasternal long axis view, tenting area and tenting distance of mitral valve was markedly increased (3.75 cm^2 and 1.21 cm, respectively). He underwent valve replacement surgery and pergolide treatment was immediately discontinued. The follow-up echocardiogram after surgery showed improvement of valvular regurgitation. Histopathological findings revealed fibromyxoid valvulopathy of mitral, tricuspid, and aortic valve without calcification.

Conclusion: Based on a review of literature, the patients taking high dose (>5 mg/day) of pergolide had higher frequency of PAVHD than those taking low dose (<5 mg/day). Also, cumulative dose of pergolide was higher, tenting area and distance of the mitral valve was larger. Despite low daily dose (2.25 mg/day) and low cumulative dose (2730 mg) of pergolide, our patient suffered from PAVHD and had a severe mitral regurgitation with large tenting area. We suggest a clinical cardiac assessment and echocardiographic follow-up, at regular intervals, in all patients initiating treatment with ergot-derived agents including low dosage of pergolide.

P283**Neuropsychological deficits in patients with Parkinson's disease and visual hallucinations**

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Objective: To evaluate cognitive functions related with the temporal lobe in non-demented Parkinson's disease patients with and without history of visual hallucinations.

Background: Neuroradiological and neuropathological studies suggest that temporal lobe has a role in the presence of visual hallucinations (VH). Parkinson's disease patients with visual hallucinations (PD-VH) show impairment in visuoperceptive skills and visual memory recognition suggestive of temporal lobe dysfunctions. In this study we tested for possible dysfunctions in other temporal functions such as language and verbal memory.

Methods: Twenty-four PD-VH were evaluated. They were compared with a group of 21 PD patients without VH and a group of healthy controls ($n = 21$). The neuropsychological examination included: Mini Mental State Examination (MMSE), Similarities (WAIS III), and Information

(WAIS III) to assess general intellectual ability; Boston Naming and Token Test to evaluate language functions; Rey Auditory-Verbal Learning Test (RAVLT) to examine verbal memory; Benton Facial recognition test and Benton Visual Form Discrimination test for visuosperceptive functions and Warrington Recognition Memory test (RMT) to evaluate visual memory.

Results: There were no differences in demographical variables (gender, age, and level of education) between controls and PD samples. PD-VH group showed an inferior visual acuity ($P = 0.019$) compared to controls and a greater score in Hamilton scale ($P < 0.05$) compared to PD and control group. Hoehn and Yahr stage was significantly higher ($P = 0.008$) in PD-VH group. PD-VH obtained a worse performance compared to controls and PD groups in MMSE ($P < 0.0005$), Boston Naming Test ($P < 0.05$), RAVLT- Learning ($P < 0.0005$), Warrington's RMT ($P < 0.0005$), Benton Facial recognition test ($P < 0.0005$) and Visual Form discrimination test ($P < 0.05$). In Token test PD-VH showed a lower execution compared to healthy control ($P = 0.001$), but there were no differences between both samples of PD patients.

Conclusions: Patients with Parkinson's disease and visual hallucinations showed several cognitive deficits related with the temporal lobe. These deficits involved not only visuosperceptive, and memory but also language functions. Our results support the involvement of temporal lobe in the pathogenesis of VH in patients with PD.

P284

Perception and expression of affective speech in Parkinson's disease
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Objective: The aim of the study is to investigate the perception and production of emotional speech in patients with Parkinson's disease (PD) by means of behavioral data, event-related potentials, functional neuroimaging, and speech analysis to learn more about temporal aspects of emotional perception, underlying neural circuits and changes in affective expression.

Background: Apart from the changes of motor functions in PD little is known about the impact of PD on the perception and production of emotional prosody even though the ability to perceive and express emotions plays a decisive role in every day social life. However, results from behavioral studies in this field show contradicting results (1,2).

Methods: Perception task: In an oddball paradigm the name "Anna" was presented pseudorandomised via headphones in neutral ($P = 0.75$), happy ($P = 0.15$) and sad ($P = 0.15$) prosody. Subjects had to judge each stimulus according to its prosody.

Expression task: Subjects had to speak the word "Anna" loudly in different emotional prosody. Additionally, patients and healthy controls underwent a neurophonetic examination.

Results: In the perception task PD patients showed a higher variation in their right answer percentage as compared to healthy controls. The event-related potentials are characterized by a P3b component for emotional target events in both groups. Interestingly, mean amplitude of the P3b appears to be smaller in PD patients. The functional neuroimaging data show for the happy and sad stimuli opposed to the neutral stimuli activity in structures known to be part of the dopaminergic system.

Taken together, behavioral data, event-related potentials and functional neuroimaging point at an altered perception of emotional prosody in PD patients.

In the expression task speech analysis, emotional expression from each subject was compared to the individual performance in the neurophonetic examination. First results indicate an alteration of affective speech in PD patients, which could be not attributed to the changes of motor functions alone.

Conclusion: Our data suggest that perception and expression of emotional communication is affected in PD and may give rise to changes in therapeutic strategies in these patients and their relatives for the future.

P285

Dream content and gender in REM sleep behavior disorder in Parkinson's disease: Preliminary findings

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Objective: To determine whether dream content differs between males and females with REM Sleep Behavior Disorder (RBD) and between those with RBD and those without RBD in patients with idiopathic Parkinson's disease (PD). Secondary aim is to evaluate whether RBD is correlated with other sleep disorders and depression and anxiety.

Background: RBD is a parasomnia that is common in patients with PD. It is characterized by aggressive nocturnal behavior during REM sleep. Other sleep disorders in PD include sleep fragmentation, daytime somnolence, and nightmares. Depression and anxiety are prevalent in PD.

Methods: Subjects were consecutively recruited from a PD clinic at Memorial Hospital in Rhode Island. Questions concerning RBD, dream content, nightmares, nightmare distress scale, and a 1-month dream log were administered. The HAM-D and HAM-A and Covi Anxiety rating scales assessed for depressive and anxiety symptoms, respectively. The Pittsburgh Sleep Quality Index and Epworth Sleepiness Scale evaluated sleep quality and daytime somnolence, respectively. The Hoehn Yahr staging measured stage of PD.

Results: Preliminary data: mean age 70.8, 27% female, mean duration of PD 6.3 years, mean stage of PD 2.4; 33.3% had RBD (of which 93.8% were male), 62.5% had nightmares. Dream content of males with RBD was violent and included being chased, attacked by people and animals, and fighting the aggressor. Dream content of females was nonviolent and involved being chased but no physical confrontation. The majority of patients without RBD had dreams that involved feelings of loneliness and loss of control. RBD was significantly correlated with male gender and duration of PD ($P < 0.05$). There were trends toward association of RBD with nightmares and alcohol intake ($P = 0.058$). Depression, anxiety and duration of PD were significantly correlated with poor sleep quality ($P < 0.01$) and nightmare distress ($P < 0.05$). Nightmares were significantly correlated with daytime somnolence ($P < 0.05$).

Conclusions: Dream content differs between males and females with RBD and between the RBD and non-RBD groups. When evaluating patients with PD, it is important to take into consideration that depression and anxiety are associated with sleep disorders, since these conditions impair quality of life and are treatable.

P286

Substantia nigra hyperechogenicity correlates with clinical and genetic status

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Objective: To further evaluate (1) transcranial sonography (TCS) for preclinical diagnosis of Parkinson's disease (PD) and (2) examine asymptomatic carriers of Parkin mutations.

Background: The *substantia nigra* (SN) shows a distinct hyperechogenic pattern on TCS in about 90% of patients with PD. SN hyperechogenicity has been described in asymptomatic carriers of single heterozygous *Parkin* mutations and was suggested as a potential preclinical marker for PD susceptibility.

Methods: We investigated SN hyperechogenicity in 58 patients and controls with and without *Parkin* mutations. All study subjects underwent a detailed neurological examination. The area (aSN) and brightness of the hyperechogenic SN were calculated bilaterally. We dichotomized the aSN using the 90% percentile of the controls and assigned subjects to high versus low value groups. *Parkin* mutation status was assessed either by comprehensive screening or testing for the known mutation in individuals from a single pedigree.

Results: The study cohort comprised a total of 58 individuals (52% m; mean age: 49.0 ± 11.3 years), 24 with clinically definite and 34 without signs and symptoms of PD. Of the 24 PD patients, 6 had one mutation and 3 two mutations in the *Parkin* gene. Of the unaffected subjects, 13 carried a single *Parkin* mutation and 21 no *Parkin* mutations (controls). After

dichotomization, 21 subjects had high and 37 subjects low values of mean aSN. Regarding the clinical status, 13 (62%) of the individuals with a high mean aSN had PD, while 26 (70%) of the study subjects with low values did not show PD ($P = 0.028$). ROC analysis of PD status as predicted by aSN revealed a high sensitivity and acceptable specificity. Similarly, probands with high mean aSN values more frequently carried (one or two) *Parkin* mutations than probands with low values ($P = 0.014$).

Conclusions: Measurement of aSN only represents a valid parameter to quantify the ultrasound abnormalities of the SN. Further strengthening the notion of a potential relationship between SN hyperechogenicity and *Parkin* mutation status, a larger aSN was associated with an increasing number of mutations in our study.

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Multiple independent subthalamic rhythms in patients with Parkinson's disease

G. Foffani, A. Priori, Ardolino, Bossi, Carrabba, Egidi, Locatelli, M. Caputo, Tamma, Baselli, A. Bianchi, G. Foffani, S. Cerutti (Milan, Italy)

Objective: To test the hypothesis that the movement-related modulation of rhythms in the human subthalamic nucleus (STN) parallels their dopaminergic modulation in Parkinson's disease.

Background: Electrodes implanted for deep brain stimulation (DBS) can be used to record local field potentials (LFPs, i.e., deep EEG activity) from the targeted structures.

We recently showed rhythm-specific dopaminergic modulation of STN activity below 50 Hz.¹ Here we extended these analyses to study the movement-related modulation of STN rhythms.

Methods: LFPs were recorded from the STN of 7 parkinsonian patients (8 nuclei) before and after levodopa administration while patients executed voluntary finger movements. Electrode localization and post-operative LFP recordings were performed using the same methods as in our previous works.^{1,2} We used an adaptive autoregressive approach for studying the movement-related data.

Results: The power of the low-frequency rhythm (<7 Hz) significantly increased with movement both before (Log power change = 0.48 ± 0.20) and after levodopa (Log power change = 0.74 ± 0.34). The power of the low-beta rhythm (13–20 Hz) markedly decreased with levodopa,¹ but its movement-related modulation was inconsistent across patients. On the contrary, the power of the high-beta rhythm (20–30 Hz) did not significantly decrease with levodopa but significantly and consistently decreased with movement (Log power change = -0.32 ± 0.19).

Conclusions: These results support our hypothesis of a functional independence between different rhythms in the human STN,¹ and extend it to the differentiation between low-beta and high-beta rhythms, which are likely to represent separate "targets" for the mechanisms of action of DBS.

G.F. was partly supported by the National Parkinson Foundation (Miami FL).

References

1. Priori A, Foffani G, et al. Rhythm-specific pharmacological modulation of subthalamic activity in Parkinson's disease. *Exp Neurol* 2004;189:369–379.
2. Foffani G, Priori A, et al. 300-Hz subthalamic oscillations in Parkinson's disease. *Brain* 2003;126:2153–2163.

P288

The mechanism of action of subthalamic deep brain stimulation: A local field potential study in patients with Parkinson's disease

A. Priori, G. Foffani, Mardolino, Bossi, Carrabba, Egidi, Locatelli, Caputo, Tamma, Baselli, A. Bianchi, G. Foffani, S. Cerutti (Milan, Italy)

Objective: To study the mechanism of deep brain stimulation (DBS) action in the human subthalamic nucleus (STN).

Background: The electrodes implanted for DBS can be used to record local field potentials (LFPs, i.e., deep EEG activity) from the targeted structures. LFPs studies in parkinsonian patients revealed the presence of multiple dopamine-dependent STN rhythms, ranging from the classical

EEG frequencies¹ up to high frequencies (~300 Hz).² LFPs are therefore a good tool for studying the DBS mechanism of action at the network level.

Methods: LFPs were recorded from the STN of 4 parkinsonian patients (8 nuclei) before and after unilateral high-frequency (130 Hz) stimulation of the STN itself. We used the same methods for electrode localization, post-operative LFP recording and spectral analysis as in our previous works.^{1,2}

Results: At "off" after overnight withdrawal of dopa-therapy, the STN spectrum showed various activity patterns below 35 Hz. 10–15 min of STN DBS elicited a marked clinical improvement and significantly increased the LFP low-frequency activity (<7 Hz) (Log power change mean \pm SD = 1.11 ± 0.48 ; Wilcoxon: $P = 0.0078$, $n = 8$). Although the clinical improvement remained unchanged for at least 90–120 s after DBS, we did not find the expected decrease of beta activity (Wilcoxon: $P > 0.24$, $n = 8$).

Conclusions: The DBS-induced enhancement of low-frequency STN oscillations described in this study resembles the dopamine-induced enhancement of low-frequency activity reported previously.¹ We conclude that STN DBS locally elicits low-frequency oscillatory activity that is important for relieving motor dysfunction in Parkinson's disease.

G.F. was partly supported by the National Parkinson Foundation (Miami FL).

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1. Priori A, Foffani G, et al. Rhythm-specific pharmacological modulation of subthalamic activity in Parkinson's disease. *Exp Neurol* 2004;189:369–379.
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P289

Radicicol induces heat-shock protein expression and neuroprotection against rotenone-mediated apoptosis in SH-SY5Y cells

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Objective: To examine anti-apoptotic effects of radicicol on SH-SY5Y cells exposed to rotenone.

Background: Heat shock proteins (HSPs), such as HSP70, function as molecular chaperones and may assist proteins in folding into their native conformation and refold abnormally aggregated proteins and thus prevent cell toxicity. We hypothesize that radicicol, an HSP inducer, may exert protective role in the treatment of Parkinson's disease (PD) in which oxidative stress and mitochondrial dysfunction are associated with reduced proteasome activity and aggregation of abnormal proteins.

Methods: In the present study, complex I inhibitor rotenone was used to induce cell death in the SH-SY5Y neuroblastoma cell line, an *in vitro* model of nigral degeneration. SH-SY5Y cells were treated with various concentrations (0–10 μ M) of radicicol for 0–24 h and the induction of HSP70 protein was measured by Western blot. To observe the neuroprotective effects of radicicol, SH-SY5Y cells were pretreated with 1 μ M of radicicol for 3 h followed by the addition of rotenone at 10 μ M. To elucidate the anti-apoptotic mechanisms of radicicol, we measured the levels of P53, a major apoptotic signaling pathway, and levels of Nurr1, a bio-biomarker of dopaminergic neuron.

Results: Rotenone induced dose-dependent apoptosis within a period of 24 h in SH-SY5Y cells. These effects were mediated through activation of caspase-9 and -3, mitochondrial release of cytochrome *c* and subsequent PARP cleavage. The increase of HSP70 protein levels induced by radicicol was both time- and dose dependent. Radicicol also suppressed rotenone-induced release of cytochrome *c*, inhibited the activation of P53, and enhanced the expression of Nurr1, which resulted in significant reduction of apoptosis.

Conclusions: We show that increase in HSP70 expression in SH-SY5Y cells induced by radicicol confers SH-SY5Y cells against rotenone-induced apoptosis. Furthermore, the suppression of apoptosis was shown to correlate with inhibition of P53 and induction of Nurr1. Therefore, compounds which can induce HSP70 protein, such as radicicol, may represent potential useful neuroprotective agents. As such they may favorably modify the progression of PD and other neurodegenerative diseases associated with aggregation of misfolded proteins.

P290**Hip fractures in patients with Parkinson's disease and deep brain stimulation**

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Objective: To evaluate the effect of subthalamic nucleus deep brain stimulation (DBS-STN) therapy for Parkinson's disease (PD) on the rate of hip fracture.

Background: Patients with Parkinson's disease are particularly at risk for hip fractures, which significantly affect quality of life and morbidity. DBS-STN therapy improves many motor symptoms of PD, but less is known about its effect on mobility and the rate of hip fracture among this patient population.

Methods: We evaluated the medical records of 42 patients with Parkinson's disease who underwent DBS-STN surgery at Vanderbilt University Medical Center from October 1999 to May 2004. Five patients were lost to follow-up, and 37 patients' medical records were assessed for the dates of DBS-STN surgeries and hip fractures.

Results: Of the 37 patients, five patients (8.1%) had suffered from a hip fracture, and of those five, two occurred before (average 51 months) and three after surgery (average 3.4 months). Using a Fisher's exact test, the occurrence of the three post-operative fractures was not significant ($P = 0.251$). A previous large scale study of over 20,000 Medicare patients that found a hip fracture rate of 15.9% in PD patients compared to 5.8% of non-PD patients served as the comparison.¹

Conclusions: This study suggests a decreased rate of hip fracture in PD patients with DBS-STN (8.1%) compared to known rates in patients without the surgery (15.9%). More large-scale studies are needed to evaluate the influence of DBS-STN therapy on the occurrence of hip fractures in patients with Parkinson's disease.

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P291**Incidence of falls and fractures in Parkinsonian disorders**

D.R. Williams, A.J. Lees (London)

Objective: To determine and compare the disease-long incidence of falls and anatomical distribution of fractures reported in different Parkinsonian disorders.

Background: Falls and fractures increase with age and disturbances of gait. Parkinsonian disorders including Parkinson's disease (PD), progressive supranuclear palsy (PSP), multiple systems atrophy (MSA) vascular parkinsonism (VP) and in some cases Alzheimer's disease (AD) have varied factors that contribute to falling.

Methods: We conducted a retrospective note review of 582 cases in the Queen Square Brain Bank. Cases were divided according to pathological diagnosis and those with PSP were further divided according to clinical phenotype [Richardson's syndrome (RS) PSP-Parkinsonism (PSP-P)], excluding falls from the criteria for division. Time to first fall and anatomical distribution of fractures were compared between these groups and to a previously reported study of fractures in the elderly.¹

Results: The mean time from disease onset to first fall was lowest in RS (13 months) and was significantly shorter than the time to fall in all other diseases including PSP-P (71 months). The disease-long incidence of falls was equal in RS (97%) and PSP-P (96%) and was significantly higher than in PD (70%), MSA (72%), VP (71%), and AD (57%). Fractures were most commonly reported in RS (28%) and PSP-P (32%), significantly more than in PD (15%), MSA (11%), VP (9%), and AD (11%). Multiple fractures were significantly more common in RS (9%) than other diseases including PSP-P. Fractures of the humerus were significantly more frequent in PSP-P (12%) than PD, RS, and MSA. Compared to the general elderly population, Parkinsonian patients have a significantly lower proportion of fractures of the distal radius, humerus (except in PSP-P), and other upper extremity

bones. The proportion of hip fractures is significantly higher in PD (51% of all fractures), RS (22%), and PSP-P (38%) than in community estimates (15%).

Conclusions: Patients with PSP fall earlier, more frequently and sustain more fractures than those with PD, MSA, VP, and AD. In RS falls occur earlier and more patients have multiple fractures than in PSP-P. The proportion of hip fractures is higher in patients with PD and PSP than in controls, in whom fractures of the upper extremity are proportionately more.

Reference

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P292**Motor heterogeneity in Parkinson's disease: An epidemiological and genetic investigation**

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Objectives: (1) To define motor heterogeneity in PD in a population-based incident cohort. (2) To explore aetiopathological differences between phenotypes via a genotyping study using a novel marker potentially associated with PD risk.

Background: Tremor dominance (TD) and postural instability and gait disturbance (PIGD) have been identified as independent phenotypic motor groups in a case series.¹ TD patients are more likely to have a family history, suggesting that genetic factors are aetiologically more important in this subgroup. A recent genome wide linkage disequilibrium screen in PD has identified a novel marker, which although not convincingly associated with all forms of PD,² warrants further investigation in motor subgroups.

Methods: A population-based incident cohort of 159 IPD patients were classified in terms of motor phenotype as TD, PIGD, or mixed on the basis of tremor and PIGD scores derived from the motor subscale of the UPDRS. Multivariate regression analysis was used to compare subgroups on cognitive phenotype and quality of life assessments. Blood samples for DNA extraction were collected from this cohort and from prevalent patients to supplement numbers. Genotyping was performed using microsatellite marker D1S2886 and allele frequencies were compared for TD patients ($n = 132$), PIGD patients ($n = 164$) and controls ($n = 365$) using chi-squared calculations.

Results: TD patients have an earlier age of onset and higher frequency of affected first degree relatives than those with PIGD and mixed phenotypes. In terms of quality of life assessments, TD patients report a greater sense of stigma whereas PIGD patients report more impairment in mobility, ADLs and bodily discomfort. There are no significant differences in cognitive profiles between subgroups. The genotyping study revealed a significant association for marker D1S2886 in TD patients ($P < 0.03$), but less association in PIGD patients.

Conclusions: Separate motor phenotypes exist in early PD which are meaningful to patients in terms of quality of life. The hypothesis that differing aetiopathologies underlie these subgroups is supported by the finding that a novel genetic marker shows a significant level of association in TD but not PIGD patients.

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P293**Placement of the most efficient contact for treatment of Parkinson's disease in patients implanted with electrodes in the subthalamic nucleus**

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Objective: To assess the position of the most effective contact of the implanted electrode for deep brain stimulation (DBS) in the subthalamic nucleus (STN) in patients with Parkinson's disease (PD).

Background: Recently, some reports have argued that the best site for DBS of the STN is located dorsally in the zona incerta rather than within the STN itself.

Methods: We have correlated the placement of the contact conveying the maximal antiparkinsonian efficacy in 8 PD patients treated with DBS and the position of such contact with respect to the STN by recording the local field potentials through the four contacts after surgery. A sequential bipolar montage giving a total of three channels per side was used. Oscillatory activity in the STN in rest condition and the evolution of the energy changes during self-induced movements were studied by means of time-frequency (Gabor) transforms. EMG activity was recorded for signaling the beginning of movement. The study was conducted in the defined "off" and "on" medication state. It was considered to be inside the STN those contacts through neuronal (oscillatory) activity was recorded. Beside this, we considered the biggest changes in the recorded activity in relation to movement could correspond to the most efficient contact. Wilcoxon matched-pair test was used for statistic analysis.

Results: Eight patients with PD and 15 STN were studied. Twelve electrodes were programmed in monopolar and 3 in bipolar combination. In any case, the recording through the electrode used for chronic stimulation showed and oscillatory activity in the β and/or γ bands, respectively, in the off and on state, in resting condition indicating it is placed within the STN. In 8 cases the contact chosen for chronic stimulation coincided with the contact showing the biggest energy changes in relation to movement, and in 5 it was adjacent to it. In 11 of these electrodes, the active contact was in the dorsal portion of the STN.

Conclusion: The most efficient contact used for chronic stimulation in PD patients is most of the times within the borders of the STN. The dorsal area is the region where the STN stimulation conveys a higher antiparkinsonian benefit in the majority of occasions.

P294

Pesticides exposure and genetic polymorphism of paraoxonase in the susceptibility of Parkinson's disease

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Objective: To investigate the association between PON1 polymorphism, pesticides exposure, and risk of Parkinson's disease in Taiwanese population.

Background: The manifestation of Parkinson's disease (PD) is characterized by bradykinesia, resting tremor, and rigidity. The etiology of PD remains unknown. Recently several studies suggest that environmental and genetic may be related to the cause of PD. Therefore, genetic variation in xenobiotic metabolizing enzymes involved in the disposition of pesticides may increase the risk of PD. Paraoxonase I (PON1) hydrolyzes pesticides and its genetic polymorphism might increase the development of PD.

Methods: We enrolled 162 controls and 125 patients with idiopathic PD. Information was collected according to a questionnaire in face-to-face interview with subjects to obtain histories of exposures to environmental factors. Data included years of farming, drinking water sources, occupational exposures to pesticides, duration, and the initial age of the pesticides exposure. Buccal mucosa cells are collected from each Parkinson's disease patients and control. We studied PON1 polymorphism at codon 54 (L and M alleles) through PCR-based restriction fragment length polymorphism (RFLP) analysis.

Results: There were significant associations between risk of PD and exposure to pesticides (OR = 1.72, 95% CI = 1.07-2.75). We did not find any significant differences between PD and control groups regarding PON1 genotype or allelic distribution. We further investigated participants who had reported exposure to pesticides and found the frequency distribution of PON1 genotypes did not differ significantly between patients and controls.

Conclusion: Our data suggest that the present survey revealed the close relationship between exposure to pesticides and the etiology of Parkinson's disease. There were no significant differences in the distribution of PON1 genotypes between cases and controls.

P295

Is the impulsivity concept able to explain behavioral effects of subthalamic nucleus stimulation in Parkinson's disease?

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Objective: To evaluate whether acute changes in STN stimulation in PD patients have an impact on different aspects of impulsivity.

Background: Impulsivity is a global concept characterized by inability to differ or inhibit cognitive, emotional, or motor actions. It leads to a lack of control, risk taking preferences, and anticipation or planning impairments. Behavioral changes like mania and impulse control disorder have been reported in a few PD patients treated with STN stimulation. These behavioral disorders could be interpreted in terms of impulsivity. Moreover, in rodent model of PD, STN lesions increase premature responses in reaction time tasks.

Methods: Eleven patients with PD in OFF medication condition were studied, both with and without STN stimulation on two separate days, 14 ± 11 (mean \pm SD) months after surgery. We controlled STN stimulation motor effect with the UPDRS motor score, improved by $64 \pm 15\%$. The Rogers decision making test assessed impulsivity linked to reward processes and Stroop test estimated impulsivity linked to inhibition control. The Barratt self-evaluating scale measured motor impulsivity, cognitive impulsivity and planning difficulty.

Results: In agreement with a previous report patients made more self-corrected errors in the interference part of the Stroop test, but STN stimulation did not change the results of the Rogers decision-making test. The Barratt impulsivity scale was also unchanged.

Conclusion: STN stimulation induced premature responses in the Stroop test suggesting a defect in executive inhibition. However, we could not show changes in reward-linked impulsivity or self-evaluated impulsivity. The rare cases of impulse control disorder after STN surgery reported in the literature always occurred in the immediate postoperative period, whereas we evaluated patients more than 1 year after surgery. We cannot exclude that our findings would have been different in the immediate postoperative period. We conclude that long-term STN stimulation does not globally induce impulsivity, but can induce mild impairment in cognitive inhibition control.

P296

Urinary incontinence in Parkinson's disease

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Objectives: 1) To assess the prevalence and associated features of urinary incontinence (UI) in patients with PD. 2) To explore the impact of UI on disability and quality of life (QoL).

Background: UI is a common but often unrecognized symptom of PD. Recent studies have identified an association between UI and problems with gait and balance.

Methods: 306 PD patients (66% M, Mean Age 66.7 ± 11.3 , Mean Hoehn and Yahr 2.4 ± 0.9) reported their frequency of UI (answers ranged from "Not at all" to "At least once a day") and completed the SF-12 QoL scale and ADL/IADL portion of a modified Older Americans Resources and Services (mOARS) scale. Univariate and multiple regression analyses controlling for age, gender, and disease stage evaluated the relationship between UI and disability (mOARS), QoL (SF-12) and PD symptoms (tremor, rigidity, bradykinesia, gait impairment, falls, dyskinesias, fluctuations on UPDRS).

Results: The prevalence of UI was 39.5% with $25\% \geq 1 \times/\text{week}$ and $13\% \geq 4 \times/\text{week}$. Univariate analyses reveal correlations between UI and gender ($F > M$), age, stage of disease, rigidity, bradykinesia, gait, falls, fluctuations, and dyskinesias, but not tremor. Regression analyses controlling for age, gender, and disease stage revealed an association between UI and bradykinesia ($P = 0.001$), gait impairment ($P = 0.004$), and falling ($P = 0.015$) but not with tremor, rigidity, dyskinesia, or fluctuations. UI correlated with disability ($P = 0.004$) and QoL (SF-12 Physical Health subscore, $P = 0.002$).

Conclusions: UI is common in PD and associated with increased disability and reduced QoL. Patients with gait and balance impairment are more likely to have UI and should be routinely screened for UI.

P297

Effect of continuous administration of rotigotine in a rat model of dyskinesia

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Objective: To evaluate the effect of a continuous administration of rotigotine in a rat model of dyskinesia. Background: The sensitization of locomotor activity in 6-OHDA lesioned rats by L-dopa has been proposed as a model of dyskinesia.¹ Continuous dopaminergic stimulation is hypothesized to prevent the induction of dyskinesia. The new, non-ergolinic dopamine agonist rotigotine is administered clinically using a patch providing continuous drug delivery. To find out whether continuous drug supply has a lower propensity to induce dyskinesia, this rat model was used.

Methods: Rats were anesthetized and 6-OHDA (8 µg) was injected into the left medial forebrain bundle. After 29 days, the rats were given continuous rotigotine (1 mg/kg every 48 h, s.c) for 10 days, whereas controls received vehicle. Locomotor activity was recorded in a rotameter. Potential conditioning to the context and expression of the sensitized response were evaluated after a drug-free period of 3 days. The effects of L-dopa had been investigated separately.

Results: Treatment with rotigotine resulted in contralateral rotations which slightly increased from day 1 to day 3 when they reached a ceiling effect. No signs of involuntary movements were observed. Conditioning to the context was not observed. Re-treatment after a drug-free period resulted in the previous response.

Conclusions: Continuous administration of rotigotine did not induce conditioning to the context: it resulted in a minor degree of a state-dependent expression of sensitization. Provided that conditioning of rotational behavioral activity can be used as a surrogate parameter for dyskinesia in rats, this confirms that a constant dopaminergic stimulation probably does not induce dyskinesia.

Experiments were performed according to ethical principles and to the requirements of the German laws on animal experimentation. All efforts were made to minimize potential suffering.

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P298

In vivo measurement of brain monoamine oxidase B (MAO-B) activity after rasagiline treatment, using L-[¹¹C]Deprenyl and positron emission tomography (PET)

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Objectives: To evaluate the binding characteristics of rasagiline, a potent, selective, and irreversible MAO-B inhibitor, using L-[¹¹C]deprenyl PET.

Background: MAO-B inhibitors have been widely used in the treatment of Parkinson's disease. MAO-B can be imaged and quantified in the living human brain using PET and ¹¹C-labeled radiotracers. PET has been used to measure the half-life of MAO-B and to investigate binding of various drugs with the enzyme.

Methods: 3 healthy non-smoking male volunteers, not on regular medications, were evaluated. They were administered rasagiline 1 mg/day for 10 days. In addition to a pre-treatment baseline brain scan (Scan #1), 3 additional dynamic L-[¹¹C]deprenyl PET scans were acquired on each subject. The 1st post-treatment scan was performed immediately after the last rasagiline dose (Scan #2). The 2nd and 3rd scans were acquired 2–3 (Scan #3) and 4–6 (Scan #4) weeks later. Venous blood samples were obtained 30 min after tracer injection.

Results: In all subjects, the baseline scan (Scan #1) showed the highest accumulation of radioactivity in the thalamus and basal ganglia, with fairly high uptake in the cortex and cerebellum, all areas known to contain high levels of MAO-B. Minimal activity was seen in the white matter. The areas of high uptake were absent in Scan #2, where activity throughout the brain was comparable to that in white matter, presumably due to rasagiline's blocking of MAO-B. Recovery of tracer uptake was gradual; several weeks post-rasagiline treatment baseline levels were apparent in Scans #3 and #4 for one volunteer, but still incomplete for 2 subjects. Radioactivity in blood samples revealed a converse pattern to that seen in the brain: it was highest in Scan #2, corresponding to lower tracer uptake in brain in this scan.

Conclusion: Daily administration of rasagiline for 10 days prevented binding of L-[¹¹C]deprenyl, as detected in PET scans of healthy volunteers. The rate of tracer recovery was slow and compatible with the reported 40-day half-life for de novo synthesis of MAO-B. These results verify specific binding of rasagiline to human brain MAO-B in vivo and confirm the irreversible inactivation of the enzyme by rasagiline.

P299

A prospective look at events and lifestyle before the onset of Parkinson's disease

A. Ascherio, H. Chen (Boston, Massachusetts, USA)

Objective: To describe how ongoing prospective studies comprising over 300,000 people are changing our view on risk factors for Parkinson's disease.

Methods: In 1976, over 120,000 women aged 30 to 55 years joined the Nurses Health Study and started reporting in biennial questionnaires details of their reproductive history, diet, use of vitamin and hormone supplements, use of drugs, physical activity, changes in body weight, blood pressure, blood cholesterol, and newly diagnosed diseases. Most of the information collected has been extensively validated by correlating the information reported in the questionnaires with suitable biomarkers in blood or adipose tissue from subsets of participants. Further, over a third of these women have provided blood samples for genetic and serological analyses. A similarly designed investigation comprising over 50,000 men aged 40 to 75 was started in 1986. The occurrence of Parkinson's disease among participants in these studies has been actively documented over the past 16 years. More recently, a parallel effort has been started to document the occurrence of Parkinson's disease in a separate cohort of over 160,000 men and women recruited in 1992.

Results: Over 850 cases of newly diagnosed Parkinson's disease have been documented in these cohorts. Several results, many intriguing and unexpected, are emerging from these data, including:

- Cigarette smoking and use of non-steroidal antiinflammatory drugs, are related to a lower risk of PD;
- Pesticide exposure is related to an increased risk;
- Weight goes down despite increased caloric intake in the 1–2 years preceding the onset of neurological symptoms, suggesting a systemic metabolic defect;
- Caffeine intake is related to a lower risk of PD in men and in women not using hormone replacement therapy (HRT), but not in women using HRT;
- In men, but not in women, consumption of milk and other dairy products is related to an increased risk of PD, whereas vigorous physical activity in high school and college is related to a reduced risk.

Conclusions: A growing body of prospectively collected data is providing new clues on middle-age exposures that may be important in shaping the future risk of PD.

P300

Levodopa half-life with additional carbidopa in Parkinson's disease (PD) patients treated with carbidopa/levodopa and entacapone

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Objective: To assess the utility of additional carbidopa in further prolonging levodopa plasma half-life in PD patients who experience end-of-dose failure and are treated with carbidopa/levodopa and a catechol-O-methyltransferase (COMT) inhibitor.

Background: COMT inhibitors' used to prolong the levodopa plasma half-life require that the dopa-decarboxylase (DDC) pathway for levodopa metabolism is fully inhibited. Carbidopa is the DDC inhibitor currently in use in the United States. It is conceivable that, in the presence of a COMT inhibitor, the DDC pathway becomes reactivated because of surplus substrate (levodopa), and the previously sufficient dosage of carbidopa is now inadequate to effectively block decarboxylase activity. We hypothesize that increasing the amount of carbidopa with the usual dosage of carbidopa/levodopa and entacapone will increase the plasma half-life of levodopa.

Methods: One male and one female PD patient were studied. Both patients had experienced motor fluctuations and were on a treatment regimen of carbidopa/levodopa 25/100 plus entacapone 200 mg. After screening, each patient was instructed not to take any medication after midnight prior to the study visit. On the first visit they received their usual combination of carbidopa/levodopa 25/100 with 200 mg of entacapone. On the second visit, 1 to 2 weeks later, the same combination of medications were administered with the addition of 50 mg of carbidopa. Levodopa levels at each visit were obtained at time 0, 30 min, 60 min, 120 min, 210 min, and 300 min.

Results: For each subject, baseline levodopa plasma half-lives were 4.0 (95% C.I.: 2.7–7.3) h and 1.8 (95% C.I.: 1.4–2.5) h. With 50 mg additional carbidopa, levodopa plasma half-lives were 6.4 (95% C.I.: 2.4–∞) h, or a 60% increase, and 2.5 (95% C.I.: 2.0–3.5) h, or a 39% increase, respectively. The area under the curve increased from 6.06 mg**h*/L to 8.79 mg**h*/L (a 45% increase) for the first patient and from 8.2 to 8.66 (a 6% increase) for the second patient.

Conclusions: Additional carbidopa may prolong levodopa plasma half-life in PD patients treated with a standard combination of carbidopa/levodopa and entacapone. Further studies are necessary to explore the clinical significance of this finding.

P301

Dyskinetic Parkinson's disease patients (PDP) and subthalamic nucleus (STN) oscillatory activity

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Objective: To analyze Local Field Potentials (LFP) activity from STN in PDP who developed dyskinesia in response to a levodopa challenge

Background: Recent studies focusing on basal ganglia neural rhythms suggests that dopamine can modulate the encoding information throughout changes in the synchronous activity in a population of neurones.

Methods: Fifteen PDP submitted to functional neurosurgery with deep brain stimulation were studied (8 patients suffered rest tremor during "off" and 11 developed dyskinesia in "on") All were continuously recorded (60–120 min length) at rest, from a clinical defined "off" state to a full "on" response after levodopa intake.

Fast Fourier Transform (FFT) of LFP activity from STN were analysed in search of:

- Presence of dominant frequency peaks in several frequency bands (5–10 Hz, 10–30 Hz, 60–85 Hz)
- Percent variation of the mean power of each band from "off" to "on"
- Determine changes of STN activity in relation with dyskinetic movements by means of FFT and Time/Frequency transforms (2 patients)

Results: Most patients exhibited the same pattern of LFP activity changes: From a dominant beta (10–30 Hz) oscillations in the "off" state to a higher gamma activity (60–80 Hz) in the "on." The mean power on the beta band dropped until 63% from "off" to "on." The gamma increased some about 185% along the cycle. Frequencies in the range of 5–10 Hz may have to different evolutions: A consistent peak during "off" was observed for patients with resting tremor. Patients with dyskinesia showed an increase about 273% of the power in this lower band coinciding with the dyskinetic movements.

There was not a change in the oscillatory behaviour locked to averaged dyskinetic movements.

Conclusions: - Increasing lower (5–10 Hz) band and hyper-gamma (>60) band, are the most striking features of oscillatory activity of STN in dyskinetic PDP in "on."

- The absence of changes locked with dyskinetic movements suggests that neuronal activity associated with dyskinesia in the STN seems to be more an oscillatory "state" than a movement related change.

P302

Tamoxifen, a protein kinase C isoform inhibitor, improves levodopa-induced motor complications in animal models of PD

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Objective: To evaluate the contribution of selective striatal PKC isoform activation to the development of levodopa-induced motor complications, we examined the ability of the PKC antagonist tamoxifen to prevent as well as reverse the shortening of motor response duration occurring in 6-hydroxydopamine lesioned rats and reduce levodopa-induced dyskinesias in MPTP-lesioned cynomolgus monkeys.

Background: The altered motor responses that complicate dopaminergic treatment of Parkinson's disease (PD) appear to involve sensitization of striatal ionotropic glutamatergic receptors. Recent evidence suggests that glutamate receptor sensitization reflects, in part, changes in the phosphorylation state of NMDA and AMPA receptor subunits due to the aberrant activation of certain serine/threonine kinases including protein kinase C (PKC). Chronic intermittent levodopa treatment of parkinsonian rats sufficient to induce response shortening of the type found in human motor fluctuations is associated with a selective increase in the expression of PKC isoforms, PKC lambda, and epsilon; gene transfer of constitutively active PKC into striatal medium spiny neurons accelerates onset of these levodopa-induced motor response alterations.

Methods: Tamoxifen was used at the dose of 5 and 7.5 mg/kg p.o. in a total of 18 6-hydroxydopamine lesioned rats and at 0.3, 1, and 3 mg/kg s.c. in 5 MPTP-lesioned cynomolgus monkeys.

Results: In rodents, pharmacological blockade of PKC with tamoxifen (5 mg/kg p.o., n = 6) diminished the levodopa-induced truncation of response duration ($P < 0.05$) and as a single administration (5 and 7.5 mg/kg p.o., n = 6 each group) reversed the response shortening ($P < 0.05$). In primates, tamoxifen alone had no effect on parkinsonian signs nor did it alter the antiparkinsonian response to levodopa. In combination with dyskinesiogenic doses of levodopa, however, tamoxifen (0.3, 1, and 3 mg/kg s.c.) reduced the severity of dyskinesias by 21, 61, and 55%, respectively ($P < 0.05$).

Conclusions: These results suggest that activation of specific PKC isoforms contributes to the striatal neuronal dysfunction underlying the motor complication syndrome and pharmacological blockade by systemically administered tamoxifen might improve the treatment of PD.

P303

The probability of the diagnosis of Parkinson's disease can be estimated by comparison of middle-latency auditory evoked responses and transcranial ultrasound

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Objective: To develop an objective measure that estimates the probability of the diagnosis of Parkinson's disease.

Background: No objective tests exist to confirm the diagnosis of Parkinson's disease. Previous work demonstrated increased midbrain echogenicity in patients with Parkinson's disease using transcranial ultrasound.¹

Methods: 42 adult volunteers between the ages of 50 and 80 years old both with and without Parkinson's disease underwent auditory evoked middle latency potential testing and transcranial ultrasound examination of the midbrain.

Results: Parkinson's patients generally have increased substantia nigra echogenicity. During this study, we noted the absence of the auditory evoked middle latency potential Pa in 67% of Parkinson's patients, and 29% of controls. Statistical comparison of auditory-evoked middle latency potential and ultrasound results suggest high and low probability of diagnosis groups. Differentiating between these groups is the presence or

absence of auditory evoked middle latency potentials. The degree of echogenicity in cm^2 yields the statistical probability of having the disease.

Conclusion: Our work suggests that the probability of the diagnosis of Parkinson's disease may be estimated by comparing these two tests. Further study is needed to determine if this technique can predict the development of Parkinson's disease in asymptomatic individuals or confirm an existing clinical diagnosis (Figures 1,2).

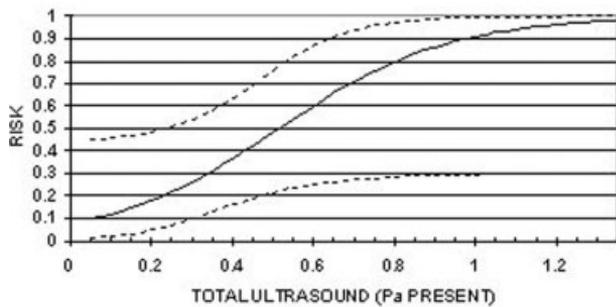


Figure 1. Abstract 303

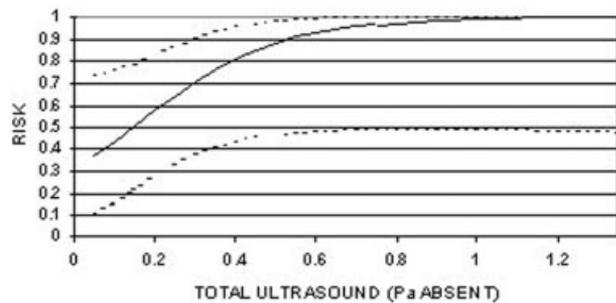


Figure 2. Abstract 303

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P304

Deep brain stimulation in Parkinson's disease: a meta-analysis of patient outcomes

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Objective: To perform a meta-analysis of the relative effectiveness of bilateral deep brain stimulation (DBS) of the subthalamic nucleus and globus pallidus on patient outcomes.

Background: DBS to treat advanced Parkinson's disease (PD) has involved two anatomical targets; the subthalamic nucleus (STN), and the globus pallidum interna (GPI). Despite the paucity of data directly comparing STN and GPI DBS, many clinicians already consider STN the preferred site.

Methods: We conducted a Medline search using Parkinson's disease, deep brain stimulation, subthalamic nucleus, globus pallidum MESH terms, supplemented with an FDA report bibliography that reviewed bilateral DBS of STN and GPI literature. We also reviewed references from these articles for additional articles. Inclusion criteria included: idiopathic Parkinson's disease, DBS of STN or GPI, UPDRS motor function scores

off medications at baseline and off medications/on stimulation at follow-up, and follow-up at least 3 months post-DBS. 31 STN and 14 GPI studies meet these criteria. The primary outcome of interest was UPDRS Part-III off medication/on stimulation state. Other outcomes included UPDRS activities of daily living subscale (ADL; part II) and levodopa equivalents before and after DBS.

Results: Motor function improved significantly following stimulation (54% for STN; 40% for GPI), with effect sizes of 2.59 and 2.04, respectively. After controlling for participant and study characteristics, STN and GPI subjects had comparable improved motor function following surgery ($P = 0.094$). Activities of daily living also improved significantly for both targets (40%). Medication requirements were significantly reduced for STN ($ES = 1.51$), but did not change for GPI subjects ($ES = -0.02$).

Conclusions: Motor function improves significantly after DBS, regardless of site, although the effect was greater, but not statistically significant in STN vs. GPI. Medication was reduced following STN DBS but did not change for GPI subjects. These results should be interpreted cautiously because they are based on non-randomized studies with small sample sizes and limited follow-up. This analysis highlights the need for a large randomized controlled trial of STN and GPI DBS to evaluate the effectiveness of DBS targets on multiple patient outcomes over time.

P305

A comparison of best medical therapy and DBS for treatment of PD: Baseline characteristics

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Objective: To compare effectiveness of STN and GPI DBS in attenuating PD symptoms at 2 years; and effectiveness of best medical therapy (BMT) to DBS in improving symptoms at 6 months.

Background: Studies indicate that STN and GPI DBS ameliorate PD symptoms; however, whether DBS is superior to BMT, benefit is maintained, or which DBS site is better is unknown.

Methods: This study will enroll 316 patients at 16 sites (7 VA; 9 university) over 3 years. Patients are randomized to BMT or immediate DBS. BMT subjects receive medical therapy for 6 months before surgery. All patients are randomized to STN or GPI DBS and followed 2-3 years. 6-month outcome is time "on" without troubling dyskinesias; 2-year outcome is UPDRS off meds/on stim. Secondary outcomes include UPDRS ADL, PDQ-39, SF-36, QWB, health resource use, complications, neuropsychological tests, and medication use.

Results: 179 patients (102 VA; 79 university) have been enrolled. Mean age is 62.9; mean time with PD is 12.3 years, 20% are women. Mean UPDRS baseline score off meds is 45.5. University and VA patients are similar on demographic and baseline clinical characteristics, with the exception of a lower female to male veteran ratio. Veterans scored lower on neuropsychological tests assessing auditory working memory, verbal associative fluency and learning, and visuomotor speed ($P_s < 0.03$) despite matching on age and education. Differences may be attributable to gender differences in psychometric performance previously demonstrated in neurologically healthy adults. Auditory working memory and verbal learning scores were lower among males, even within the University sample ($P_s = 0.04; 0.009$). However, male veterans performed lower than male University subjects on verbal learning/memory task and verbal associative fluency at baseline ($P_s < 0.03$).

Conclusions: Study participants are older (62 years) than reported in prior DBS studies (56 years), suggesting that findings may be more generalizable. Baseline demographic and clinical differences are small, but some differences in neuropsychological performance are noted between veterans and university subjects. Of interest is whether within and between groups variability in baseline characteristics (including neuropsychological functioning) relate to outcomes. Results expected in 2007.

P306**Mechanisms of unilateral STN-DBS in patients with Parkinson's disease: Why effects are bilateral?**

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Objective: To elucidate mechanisms for therapeutic effect on bilateral symptoms by unilateral deep brain stimulation (DBS) of the subthalamic nucleus (STN) in patients with Parkinson's disease (PD).

Background: It is well known that bilateral symptoms and signs are often improved by unilateral DBS. However, it remains to be studied why such bilateral effects are produced by unilateral stimulation. The aim of this paper is to study effects of unilateral STN-DBS with positron emission computed tomography (PET) and find out why bilateral improvement is induced.

Methods: We conducted F-DOPA and F-FDG PET scans in 8 PD patients in whom unilateral STN-DBS improved bilateral limb symptoms and axial symptoms (gait and axial signs). Their mean age was 54 years and duration of illness was 10 years. Both scans were performed when DBS was on and when DBS was off for about 1 day. We compared PET images between DBS on and off using statistic parametric mapping (SPM) method.

Results: Significant improvement was elicited by DBS in total Unified HD Rating Scale (UPDRS) (30 ± 12 to 14 ± 7), bilateral limb scores, axial and gait scores. F-DOPA PET showed no significant differences between DBS on and off. In contrast, FDG PET revealed that STN-DBS evoked significant metabolic increase in the ipsilateral VPL and VPM nucleus of thalamus. Moreover, deactivation occurred at the contralateral internal globus pallidus (GPI) and ipsilateral parahippocampal gyrus.

Conclusions: Ipsilateral thalamic activation must cause ipsilateral motor cortical activation, which finally explains the improvement of contralateral limb symptoms. Deactivation of the contralateral GPI must disinhibit the contralateral thalamus and contralateral motor cortex, which finally explains reduction of ipsilateral limb symptoms. Bilateral basal ganglia functional improvement should explain axial symptoms improvement. Parahippocampal deactivation may explain an intellectual decline often seen as an adverse effect of DBS. We give some clues why bilateral symptoms are improved by unilateral DBS.

P307**Low dose aripiprazole for the treatment of drug induced psychosis (DIP) in Parkinson's disease (PD) patients**

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Background: Drug induced psychosis affects 5–8% of PD patients. Partial dopamine agonists, such as aripiprazole have a theoretical role in managing this problem as they may control psychosis without harming motor function.

Objectives: to evaluate low dose aripiprazole as a potential treatment for DIP in PD.

Methods: Fourteen mildly or non demented PD patients with drug induced psychosis from 5 sites were enrolled in a 6-week open-label study of aripiprazole (starting at 1 mg/d, titrated weekly as needed to a ceiling dose of 5 mg/d) to treat DIP in PD patients. Subjects were evaluated using standard PD instruments for motor function, the neuropsychiatric inventory (NPI), the brief psychiatric rating scale (BPRS), and the clinical global impression scale (CGI) for psychotic symptoms. Last observation carried forward methods were used for analysis.

Results: Eight women and 6 men with a mean age of 74 enrolled. At entry the median Hoehn-Yahr stage was 3.0 (range 2–4), mean UPDRS motor score 34 (SD = 3.1) and the mean mini-mental status exam score was 26.4 (SD = 0.7). "Core BPRS" improvement of $\geq 25\%$ occurred in 6, with no significant change in 4, and worsened psychosis in 4. Six subjects completed 6 weeks of treatment of whom 5 continued into an extension phase. Eight patients discontinued early (at study days 8, 8, 9, 11, 14, 18,

32, 35), due to: worsened parkinsonism (n = 3), worsened psychosis (2), worsened parkinsonism and psychosis (2), and lack of efficacy (1). Seven subjects suffered a decline of ≥ 10 points in the Schwab and England activities of daily living. Pooled data analysis revealed statistically significant improvement on the mean total score of the Brief Psychiatric Rating Scale (BPRS), as well as the "positive" symptoms total of the BPRS and the hallucinations score.

Conclusion: In this preliminary investigation, aripiprazole exhibited minimal benefit based on the high drop out rate, aggravated parkinsonism in some patients, and variable effect on psychotic symptoms.

P308**Developing a measure of communicative effectiveness for individuals with Parkinson's disease (PD)**

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Objective: To investigate whether the Communicative Effectiveness Survey (CES) demonstrated sufficient psychometric properties for use as a functional communication measure for PD patients.

Background: Approximately 70% of PD patients develop motor speech disorders from mild to severe. There is a paucity of research investigating the impact of movement and communication disorders on PD patients' ability to participate in life roles. In a prior study using Rasch analysis (an item response theory), the CES demonstrated more than adequate measurement properties in a group of 95 subjects with movement disorders (speech competency range-normal to severe dysarthria). This report's purpose is to analyze the responses of the PD patients who participated in the original study.

Methods: Subjects—66 idiopathic PD patients diagnosed by a movement disorders neurologist. Average UPDRS motor score—35.44 (range 0–77). Speech competency ranged from normal to severe dysarthria. Patients rated communicative effectiveness in 8 common speaking situations, on a 7-point rating scale on the CES. A speech pathologist blind to the purpose of the study and method of data analysis collected data. MINISTEP computer software performed Rasch analysis.

Results: Subjects average age—66.5 years (range 18–87), and gender distribution—64% male. Raters used 3 of 7 rating scale units with such low probability that a 4-point rating scale was used for analyses. Goodness of fit statistics of 0.99 for persons and 0.98 for items (ideal MnSq = 1) indicated an "expected" pattern of responses to the CES (those with mild dysarthria rated communicative effectiveness higher than those with severe dysarthria). Person ability and item difficulty calibrations were within two standard errors indicating that the CES was well matched to the sample. The order of item difficulty matched the theoretical hierarchy proposed prior to the study (speaking at home was easier than speaking in public). Person separation reliability 0.92 (analogous to Cronbach's alpha) was high.

Conclusion: The CES has adequate measurement properties to use in the development of a measure of communicative effectiveness for PD patients. We foresee doctors and clinicians welcoming a precise measure of a PD patient's ability to participate in functional speaking situations.

P309**Motor evoked potentials are less facilitated after contralateral homologous muscle activation in Parkinson's disease**

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Objective: To assess whether contralateral homologous hand muscle activation involves changes in motor cortex function in Parkinson's disease (PD).

Background: Transcranial magnetic stimulation (TMS) preferentially activates corticospinal neurons transsynaptically within the primary motor cortex. TMS can be used to quantify motor cortical physiology in Parkinson's disease. Motor cortex stimulus–response curves plot the amplitude or area of the Motor Evoked Potential (MEP) at a range of different stimu-

lation intensities. These curves can be used as a measure of motor cortex excitability.

Methods: This was an observational cohort study. Thirty patients with PD and 7 age matched controls were recruited from the outpatient clinic. Patients with epilepsy were excluded. Clinical evaluation was done using Unified Parkinson's Disease Rating Scale (UPDRS). Single pulse technique using Magstim 200 stimulator was used. For data analysis, the profile was summarised using threshold and slopes of the curve.

Results: In healthy controls, activation of the contralateral homologous muscle produced a fall in threshold ($P = 0.002$). However, in patients with PD, activation failed to produce a fall in threshold. The slope of the stimulus-response curve plotted from the right abductor pollicis brevis muscle was higher during activation of the contralateral homologous counterpart compared to the slope in the resting state in healthy controls ($P = 0.04$). A similar response was seen in patients with PD ($P = 0.03$). However, patients with PD, activation of the abductor pollicis brevis resulted in a significantly smaller increase in the MEP area compared to the controls. The threshold did not change as a function of "ON"/"OFF" states. There was no difference in the slopes of the stimulus-response curves between the "OFF" and "ON" states.

Conclusions: We observed reduced MEP facilitation in response to contralateral homologous muscle contraction in PD. This may represent abnormal function of cortical motor neurons during voluntary muscle contraction. Dopaminergic drugs do not affect MEP amplitudes in patients with PD. This study further supports the hypothesis that the primary motor cortex may play a central role in the pathophysiology of PD.

P310

Long-term efficacy of istradefylline in patients with advanced Parkinson's disease

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Objectives: Current dopaminergic therapies for Parkinson's disease (PD) are associated with problematic long-term tolerability and response durability. Adenosine A_{2A} receptors are a promising non-dopaminergic target for treating PD. We report here the long-term efficacy of istradefylline, an adenosine A_{2A} receptor antagonist, in patients with advanced PD not optimally controlled with levodopa therapy.

Methods: This was a long-term, multicenter, open-label study in subjects previously enrolled in double-blind, placebo-controlled studies of istradefylline. Istradefylline dosage was 40 mg/day and could be adjusted down to 20 or up to 60 mg/day. Efficacy was evaluated by patient diaries to record awake time in the OFF state.

Results: The intent-to-treat population was 496 patients. Subjects were classified in 2 groups for efficacy analysis: those exposed to istradefylline in a preceding double-blind study (Group 1; $n = 315$), and those exposed to placebo in a preceding double-blind study plus those who had not been treated with study drug (active or placebo) for >2 weeks since a preceding double-blind study (Group 2; $n = 181$). Demographics for the 2 groups were similar. Efficacy results previously reported from double-blind studies show that 40 mg/d istradefylline is associated with a 1.1-h reduction in total OFF time at 12 weeks. Group 1 subjects in this study entered with approximately 1.2 h less total OFF time than did Group 2 subjects (4.4 h vs. 5.6 h). Total hours of OFF time in Group 1 remained stable up to 52 weeks of treatment. Group 2 patients had a reduction in OFF time of ~0.7–0.9 h starting within 2 weeks of istradefylline treatment and continuing up to 52 weeks. The magnitude of reduction in OFF time was similar to that recorded in previous placebo-controlled, double-blind trials.

Conclusion: Subjects on istradefylline at entry into an open-label study maintained stable total hours of OFF time during long-term usage (with some exposed longer than 52 weeks). Subjects on placebo at the time of entry into this study, or those who had not received study drug treatment for >2 weeks since a preceding placebo-controlled, double-blind study, entered with more total hours of OFF time but showed a prompt reduction of 0.7–0.9 h in OFF time on open-label istradefylline that was maintained up to 52 weeks of treatment.

P311

Rotigotine transdermal patch (Neupro®) is efficacious and safe in patients with early-stage, idiopathic Parkinson's disease, regardless of gender, age, duration and severity of disease. Results of a multicenter, randomized, double-blind, placebo-controlled trial

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Objectives: To investigate the efficacy of rotigotine in different subgroups of subjects with early-stage Parkinson's disease, based on their gender, age, disease severity, and duration.

Methods: This was a multicenter, randomized, double-blind, placebo-controlled trial in patients with early-stage, idiopathic Parkinson's disease (Hoehn Yahr stage ≤ 3). Starting at 4.5 mg/day (10 cm^2), patients were titrated weekly in 4.5-mg increments to an optimal dose up to 13.5 mg/day (30 cm^2) and were maintained at this dose for 6 months. The primary efficacy measure was the change from baseline to the end of treatment in UPDRS subtotal (parts II + III). This parameter was analyzed based on gender, age, severity and duration of disease.

Results: 273 subjects were used for the analysis (177 treated with rotigotine and 96 with placebo). The rotigotine group showed an overall significant improvement in the UPDRS subtotal score from baseline to the end of maintenance phase compared with placebo (Rotigotine: -3.8 , placebo: 1.5 , $P < 0.0001$). Both genders showed a similar benefit from rotigotine treatment compared with placebo at the end of maintenance phase (males: -4.5 vs. $+1.3$, females: -2.4 vs. 1.7 points). Similarly, there was no clinically relevant difference in treatment benefit from rotigotine depending on the subjects' age (subjects <65 years of age: -4.8 vs. 2.4 ; subjects 65–74 years of age: -2.2 vs. 0.4 ; subjects > 75 years of age: -2.2 vs. 1.3 points). Disease severity (baseline subtotal UPDRS II + III scores) and Parkinson's disease duration did not affect the efficacy of rotigotine compared to placebo (baseline UPDRS subtotal score <30: -3.5 vs. 1.9 ; baseline UPDRS subtotal score ≥ 30 : -4.1 vs. 1.0 ; Disease duration <1 year: -4.7 vs. 0.3 ; disease duration ≥ 1 year: -2.9 vs. 2.4 points).

For the majority of subjects, rotigotine was generally well-tolerated. The safety profile was not affected by age, gender, disease severity, or duration.

Conclusions: Rotigotine was effective and well-tolerated for the treatment of early-stage Parkinson's disease up to a dose of 13.5 mg/day (30 cm^2), independent of age, gender, disease severity, and duration.

P312

Fluctuations in gait force profiles in patients with Parkinson's disease

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Objective: To study the fluctuations in gait, as expressed by the ground reaction force profiles in patients with Parkinson's disease (PD) and in elderly subjects.

Background: Gait analysis is used to augment the diagnosis and prognosis of various neurological diseases. For example, increased stride-to-stride variability has been shown to be associated with PD. Here we study another aspect of gait and its relation to PD by examining the shape of the force profile of the ground reaction force during the stance phases of walking. By using Detrended Fluctuation Analysis (DFA), an analytical tool developed by statistical physicists to investigate complex systems, we investigate the fluctuations in the shape of consecutive force profiles. DFA enables the study of the fluctuations in different time windows ("scales"), where each scale represents the resolution at which we consider the fluctuations, and the correlations across time.

Methods: 10 PD patients (HY scale: 2–3) and 10 healthy elderly subjects wore force-sensitive insoles that recorded the normal force exerted by the floor while stepping during a period of 2 min of comfortable walking. For each leg for each step, a single force profile was plotted as function of time and normalized to a fixed number of data points during the stance phase. We generated data series corresponding to consecutive steps where each data point represents the integrated power spectra over a fixed band of

frequencies of the Fourier transformed normalized force curve. DFA was used to estimate the fluctuations in the force profile on different time scales and to study the correlation behavior of the fluctuations.

Results: Global variance of the form-sensitive time series and the local variance at all scales (3–11 data points) were significantly increased in the PD group as compared to the control group ($P < 0.05$). On the other hand, the correlation behavior of the fluctuations was not significantly different in the two groups.

Conclusions: PD lowers the stability of the force profile. The reduced stability is not just a global phenomenon but can be found at different time scales. Statistical analysis of the fluctuations of the shape of the force profiles may offer new possibilities for enhancing the quantification of PD and the understanding of its effect on gait.

P313

The relationship between visuo-motor deficits and motor UPDRS in Parkinson's disease (PD)

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It is long known that PD patients suffer from deficient visuo-motor coordination (VMC). This deficit is used to facilitate early and differential diagnosis of PD, however, its relationship to other motor deficits is still unknown. This relationship is reported in the present paper.

Thirty-nine moderate PD patients, age: 64.8 ± 11.8 years (mean \pm SD), H&Y stage 2 ± 1 , were subjected to detailed VMC testing during their standard neurological examination. VMC testing included 3 tracking tests in which the subject had to maintain a "mouse" controlled cursor within a moving target and 3 tracing tests in which the subject had to move the cursor along a path displayed on screen, with each hand (total of 12 tests). Data on tracking persistence, assimilation of target speed and proximity to target was obtained from tracking. Proximity to the model path, directional control and spontaneous velocity were obtained from tracing.

Motor UPDRS correlated strongly with tracking persistence and with target speed assimilation (Pearson correlation = 0.65, $P < 10^{-5}$ for each). Proximity to target, proximity to the path and directional control correlated moderately with motor UPDRS and tracing velocity did not correlate significantly. Detailed analysis revealed that gait, facial, axial, and to a lesser extent upper limb bradykinesia, contributed significantly to the above correlations with tracking persistence and speed, while tremor of the hand did not correlate with any of the VMC variables. These results show that VMC deficits are part of a general problem in motor/executorial capabilities, and not consequent to motor deficits of the hand.

P314

Entacapone to tolcapone switch study: Multicenter double-blind, randomized, active-controlled trial in advanced Parkinson's disease

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Objective: To assess whether tolcapone could benefit PD patients with levodopa response fluctuations despite optimal entacapone treatment.

Background: COMT inhibition increases levodopa bioavailability and half-life, resulting in better control of PD symptoms. No studies have directly compared the two licensed COMT inhibitors, tolcapone and entacapone, but clinical experience indicates that tolcapone may be more effective, although its use was restricted after 3 cases of fatal liver failure in patients whose liver function was not monitored.

Methods: Before randomization, all patients were treated with entacapone for ≥ 10 days while levodopa treatment was optimized. Those who continued to have ≥ 3 hours/day "off" time were randomized double blind to entacapone 200 mg with each levodopa dose ($n = 75$) or tolcapone 100 mg TID ($n = 75$) and were treated for 3 weeks. Efficacy measures included the proportion of patients with increased daily "on" time, change in "on" time, investigator's global assessment of improvement, and changes in UPDRS and levodopa dose. Safety measures included adverse events and laboratory tests.

Results: The effect of treatment on "on" time is shown in the table (per-protocol population). Tolcapone showed significant superiority in the

proportion of patients with ≥ 3 hours/day "on" time and the overall change in "on" time, and a trend toward superiority in other end points, even with the unexpected improvement in the entacapone group, which should have been optimally treated before randomization (Table). Dyskinesia was the

TABLE 1. Abstract 314

Patients with increased "on" time	Entacapone	Tolcapone	P
3 hours	11.7%	29.0%	0.02
1 hour	46.7%	58.1%	0.21
Change in "on" time (hr/day)	0.8	1.6	0.04

most common adverse event in both groups (entacapone 29%, tolcapone 31%, NS). One marked laboratory abnormality was seen (raised liver enzymes in a tolcapone patient with a history of alcoholism), which resolved on treatment withdrawal. One patient on entacapone stopped treatment because of raised liver enzymes.

Conclusion: The data show a clear trend for enhanced efficacy with tolcapone in advanced PD patients when they were switched from entacapone. The safety profile of the two drugs was similar. These results contributed to the lifting of the suspension of tolcapone in Europe.

P315

Entacapone significantly decreases elevated plasma homocysteine levels in levodopa-treated Parkinson's disease patients

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Objective: To assess the effect of entacapone, a peripherally acting catechol-O-methyltransferase (COMT) inhibitor, on plasma levels of homocysteine in levodopa-treated Parkinson's disease (PD) patients.

Background: Hyperhomocysteinemia has been associated with several disease conditions including vascular diseases. A common cause is folate or vitamin B12 deficiency, but this does not explain the elevated homocysteine levels reported recently in levodopa-treated PD patients. Levodopa is metabolized by COMT leading to the subsequent formation of homocysteine. It is therefore rational to predict that COMT inhibition by entacapone would result in reduced homocysteine levels and recent pre-clinical findings support this hypothesis. The overall risk for vascular diseases associated with hyperhomocysteinemia has been well established but the vascular risk associated with elevated plasma homocysteine levels in levodopa-treated PD patients remains controversial. However, a recent clinical study established an increased risk for coronary artery disease in the levodopa-treated patients compared with those not treated with levodopa.

Methods: Plasma homocysteine levels were analyzed in 44 levodopa-treated PD patients with motor fluctuations that were randomized to placebo in a 6-month, placebo-controlled, double-blind study, and switched to open-label entacapone for the follow-up study. Plasma samples were collected at baseline of the follow-up study (before switching to open-label entacapone) and after 1 year of follow-up on entacapone. Aliquots of the plasma were kept at -70°C and homocysteine levels were subsequently analyzed. The mean duration of PD was 12.8 years and the mean daily levodopa dose 782 mg.

Results: The mean plasma homocysteine concentration at 1 year after initiation of entacapone treatment (15.9 ± 5.9 , mean \pm SD) was significantly lower compared with baseline (17.3 ± 6.1 , mean \pm SD) ($P < 0.01$).

Conclusion: The findings of this exploratory analysis indicate that introducing entacapone significantly decreases elevated plasma homocysteine levels in levodopa-treated PD patients. Further studies are warranted to assess whether the addition of entacapone may contribute to a lower incidence of vascular complications in levodopa-treated PD patients.

P316

Bilateral coordination of gait is impaired in patients with Parkinson's disease prone to freezing

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Objective: To study bilateral coordination of gait in patients with freezing of gait (FOG) and Parkinson's disease (PD).

Background: FOG is a disabling phenomenon in the advanced stages of PD. The etiology of FOG is unclear. Recent studies suggested that the gait of PD patients prone to FOG (PD + FOG) is: 1) less rhythmic; and 2) more asymmetric, as compared to the gait of PD patients who do not experience FOG (PD - FOG). Therefore, we hypothesized that impaired bilateral coordination of gait may be related to FOG.

Methods: 20 and 11 PD + FOG and PD - FOG patients, respectively (HY scale 2.5-3.5), were tested during "Off" (unmedicated), and again during "On" (medicated), state. Force-sensitive insoles were used to record the timing of each gait cycle during comfortable walking. Bilateral coordination of gait was evaluated by the phase relationship between left and right heel-strikes with respect to the stride cycle duration (normalized to 360°). For each subject the leg with the shorter average swing time was identified and the mean phase of that leg stepping was calculated. The coefficient of variation of the phase (Phase_CV) was calculated to evaluate the variability in phase generation, and the mean of the absolute difference between the phase and 180° (ABS_Phase) was calculated to evaluate accuracy of phase generation.

Results: PD + FOG and PD - FOG patients had almost identical mean values of phase, i.e., $179.9 \pm 7.9^\circ$ (SD), during "Off" and "On" states. During the "Off" state, Phase_CV and ABS_Phase were higher in PD + FOG compared to PD - FOG. Mean (\pm SE) Phase_CV values were $10.0 \pm 2.7\%$ and $3.9 \pm 0.4\%$ for PD + FOG and PD - FOG, respectively ($P = 0.022$). Mean (\pm SE) ABS_Phase values were $16.3 \pm 4.5^\circ$ and $6.1 \pm 0.8^\circ$ for PD + FOG and PD - FOG, respectively ($P = 0.036$). During the "On" state, group differences for Phase_CV and ABS_Phase were not statistically significant ($P > 0.1$). For both variables and groups, the medication effect was not statistically significant ($P > 0.1$).

Conclusions: PD + FOG patients are less able to accurately and consistently coordinate the timing of left and right feet stepping during walking. While it remains to be seen if this impairment is in the causal pathway of FOG, the present findings suggest the potential merit for further investigation of this question.

P317

Selegiline diminishes cardiac sympathetic nerve function by MIBG scintigraphy

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Objective: To reveal effects of selegiline on cardiac MIBG scintigraphy.

Background: Selegiline sometimes causes orthostatic hypotension in PD treatment. Selegiline is metabolized to l-methamphetamine that has effects to inhibition of reuptake of norepinephrine (NA) and, facilitate to NA release from sympathetic nerve terminals.

Methods: We investigate cardiac MIBG scintigraphy before and after selegiline administration (5 mg/day) in 28 PD patients (mean age; 64.5 y-o, Hoehn & Yahr stages 1-3). Cardiac MIBG scintigraphy was performed at 15 min and 4 h after MIBG intravenous injection. Heart (H)/Mediastinum (M) ratio was evaluated. Selegiline was administered for 14-120 days. All drugs were not changed during selegiline treatment. The IRB of hospital approved this study. Informed consents were obtained from all patients.

Results: MIBG uptake of both early phase (15 min) and late phase (4 h) after selegiline treatment were significantly decreased compared with those before treatment. No cardiovascular adverse events were not observed by selegiline treatment.

Conclusion: Selegiline treatment significantly inhibited uptake of MIBG at cardiac sympathetic terminals. This effect was supposed to be caused by l-methamphetamine of selegiline metabolite. Daily 5 mg administration of selegiline caused significantly inhibition of cardiac sympathetic function in PD, but clinically no cardiovascular symptoms and signs including ortho-

TABLE 1. Abstract 317: Values are mean (SD)

	Early H/M ratio	Late H/M ratio
Before Tx	1.98 (0.34)	1.82 (0.51) 1.40 (0.19)*
After Tx	1.71 (0.26)*	* $P < 0.001$

static hypotension or dizziness. We should pay attention to cardiovascular functions and evaluation of the results of cardiac MIBG scintigraphy when we treat PD with selegiline.

P318

Progressive deterioration in quality of life of untreated Parkinson's patients over 18 months clinical follow up: Results from PDLIFE, a multi-centre prospective study of 401 patients

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Aims: A multicentre (15) observational study to serially assess changes in quality of life (QOL) in untreated (drug naïve) Parkinson's disease (DNPd) and those on monotherapy (MTPD) over a 3-year period across the UK. To our knowledge, this is the first study addressing this issue.

Background: At diagnosis, PD patients may be left untreated and treatment is started when the disability progresses. The effect of this "wait and watch" strategy on the quality of life (QOL) of patients left untreated is unknown.

Methods: Using a standard proforma, anonymised data have been collected including demographic details, drug histories and QOL (PDQ 39) in DNPd and those on monotherapy since 2001. Follow up assessments take place 0.5-1 yearly intervals.

Results: 401 (172 DNPd and 229 MTPD) PD patients (mean age 66.3 years; Hoehn and Yahr (HY) 1.74; 40% females; mean duration PD 4 years) have been entered to PDLIFE. At first follow-up (FU) after a mean 10.5 months, out of 172 DNPd, 30 were left untreated. In this group, there was a significant deterioration in overall QOL ($P < 0.01$) in comparison to those in whom treatment was started. In DNPd patients deterioration in QOL was seen in 8/8 domains of the PDQ 39. At second FU, after a mean period of 18.5 months, 10 continue to remain untreated with a further significant deterioration in overall QOL ($P < 0.05$) in comparison to MTPD who report no significant change in overall QOL ($P > 0.05$). In 57 of the initial 172 DNPd, started on dopaminergic treatment there was a significant improvement in overall QOL ($P < 0.05$) at second FU.

Conclusions: This data, collected for the first time in untreated PD, indicates that in the UK, approximately 10% of patients with PD referred to specialist clinics are not given treatment. QOL of such patients deteriorate significantly the longer they are left untreated, unlike those treated. This data questions the merits of a "watch and wait strategy" for treating PD and highlights the use of quality of life measures to assess outcome of treatment in PD.

P319

Cognitive impairment in Parkinson's disease correlates with hippocampal atrophy on MRI and temporal-parietal hypoperfusion on rCBF SPECT

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Objective: To assess the correlates of cognitive impairment and the hippocampal atrophy and rCBF SPECT in patients with idiopathic Parkinson's disease (PD).

Background: The pathogenesis of dementia in PD still remains unknown. The patterns of rCBF described till now are inconsistent.

Methods and material: 60 (F25, M35) patients with PD (mean age 68 ± 7.25) were included and divided into 3 groups according to severity (psychological testing: MMSE, verbal fluency, verbal and non-verbal memory, depression, executive functions, and DSM-IV criteria) of cognitive impairment: with no impairment (I, $n = 17$), mild cognitive impairment (II, $n = 25$) and dementia (III, $n = 18$). The groups significantly differed in terms of age (gr.III was older), disease severity (UPDRS, Hoehn-Yahr), but not of age at onset, disease duration, and depression. The hippocampal atrophy on MRI was measured using Scheltens et al. visual rating scale and rCBF SPECT was performed with the use of Tc-99m-ECD. The rCBF was compared between the groups and controls ($n = 20$).

Results: The hippocampal atrophy was more pronounced in groups II and III, but statistically significant was only the difference between group III and I ($P < 0.05$). rCBF SPECT revealed the hypoperfusion in all selected areas when compared to controls, but within groups (III vs II and I) the most severe hypoperfusion was noticed in left temporal and parietal regions ($P < 0.05$). Using the step-wise regression analysis the left temporal hypoperfusion and left thalamus hyperperfusion were found the best predictors of dementia with positive prediction value within group I: 94.1% and group III: 88.9%. The left temporal hypoperfusion significantly ($P < 0.01$) correlated with left hippocampal atrophy on MRI.

Conclusions: Hippocampal atrophy and left temporal hypoperfusion characterized the group of PD with dementia. This pattern may resemble the findings in Alzheimer's Disease and/or Dementia with Lewy Bodies, although in the latter one the findings in rCBF SPECT are inconsistent. This may suggest the co-existent or overlapping pathology (due to, e.g., increased age: PD + AD + DLB) responsible for cognitive impairment in PD.

P320

Urinary 8-hydroxyguanosine levels as a biomarker for progression of Parkinson's disease

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Objective: To evaluate whether or not 8-OHdG is a useful biomarker for the disease process.

Background: It is important to develop the biomarkers for Parkinson's disease (PD). There has been growing evidence that mitochondrial dysfunction and oxidative stress contribute the pathogenesis for PD. 8-hydroxyguanosine (8-OHdG) has been used to evaluate oxidative stress. Thus, it may be a potential biomarker for evaluating the disease. Therefore, we investigated the levels of urinary 8-OHdG.

Methods: We studied 72 patients with PD, 16 patients with MSA, and 4 normal controls. Urinary 8-OHdG was measured using an enzyme-linked immunosorbent assay (ELISA) system. The urinary samples were obtained from each subject in the morning.

Results: The range of 8-OHdG ratio were normal control: 6.61–23.18, PD: 11.90–68.69, MSA: 7.76–30.81. Urinary 8-OHdG/creatinine ratios correlated with age in normal subjects ($r = 0.61$, $P < 0.01$), but not in PD. The mean urinary 8-OHdG/creatinine ratio of PD was higher than that of age-matched control subjects ($P < 0.01$).

Conclusions: The mean urinary 8-OHdG increased with the stage of PD and was not influenced by the current dose of DOPA. Our results suggest that urinary 8-OHdG is a potentially useful biomarker for evaluating the progression of PD.

P321

Abnormalities of short afferent inhibition of cutaneous stimulation in Parkinson's disease are reversed by dopaminergic drugs

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Objective: To evaluate if medications may reverse abnormalities of sensorimotor integration in patients with Parkinson's disease (PD).

Background: Abnormal excitability of the motor system to somatosensory input has been reported in PD.^{1,2} In particular, short afferent inhibition

(SAI) to cutaneous afferents has been demonstrated to be abnormal in patients with PD.²

Methods: The effect of electrical stimulation of the fifth finger on motor evoked potentials (MEPs) to transcranial magnetic stimulation (TMS) in abductor digiti minimi muscle was evaluated in 8 PD patients off and on medication. Digital stimuli preceded TMS at interstimulus intervals (ISIs) of 20–50 ms. Sixteen healthy age-matched subjects acted as controls.

Results: Digital stimulation caused MEP reduction in normal controls (up to 38% of test MEP) and abnormal MEP potentiation in PD patients (up to 171% of test MEP) in off condition at ISIs tested ($P < 0.05$). These SAI abnormalities were partially reversed after drug administration (on condition).

Conclusions: Digital stimulation causes abnormal enhancement of motor responses in PD patients. SAI abnormalities may be reversed by L-Dopa and dopaminergic drugs. The present results support the hypothesis that abnormal processing of cutaneous inputs might contribute to the pathogenesis of parkinsonian motor symptoms.

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P322

Cabergoline versus ropinirole as add-on therapy in Parkinson's disease

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Objective: We aimed to investigate the efficacy and tolerability of cabergoline and ropinirole in add-on therapy in Parkinson's disease (PD).

Background: Dopamine agonists used in the treatment of PD bind to different receptor subtypes and they have distinct neuropharmacological profiles; therefore, they are expected to produce heterogenous clinical responses. Cabergoline is a long-acting, ergoline dopamine agonist with high affinity for D2 receptors and lesser affinity for D1 receptors, while ropinirole is a non-ergot derived D2 like agonist.

Methods: 44 patients with mild and moderate PD were randomly assigned to cabergoline and ropinirole therapy. The patients were assessed with the Unified Parkinson's Disease Rating Scale (UPDRS) weekly for the first month and monthly for the next 3 months. The criteria for the efficacy for each drug was measured with the reduction in off-state, total levodopa dosage, and the improvement in UPDRS motor and daily living activity scores.

Results: Mean UPDRS motor scores was reduced 31.22% in cabergoline group and 35.70% in ropinirole group. Total levodopa dosage was reduced from 426.14 mg to 335.227 mg (21.3%) in cabergoline group and ropinirole group showed reduction from 394.89 mg to 289.773 mg (26.66%). There was no significant difference for the reduction in off-state, total levodopa dosage and improvement in UPDRS scores for both groups ($P > 0.05$) but changes in scores over time was significant ($P < 0.05$). No serious adverse effects were observed in both groups.

Conclusions: Cabergoline and ropinirole are both effective and well-tolerated in add-on therapy in PD. Although cabergoline makes continuous dopaminergic stimulation which is compatible with physiological conditions as a result of its long half-life, its side effects are a bit higher than ropinirole. So the key factor while choosing a dopamine agonist for add-on therapy for PD should not only be the longer half-life of the drug, but also the patient's compliance.

P323

Smoking and tea consumption delay onset of Parkinson's disease, but do not affect disease progression

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Objectives: To examine the influence of cigarette smoking, coffee or tea consumption on age at onset of Parkinson's disease and its rate of progression.

Background: Previous epidemiological studies found a negative association between cigarette smoking and coffee and/or tea drinking with a prevalence of Parkinson's disease (PD). However, it is unknown how these factors affect the age of onset and the rate of the progression of the disease.

Methods: A retrospective study was conducted among 278 consecutive PD patients. Data on smoking and coffee or tea consumption were obtained through direct or proxy interviews. Multiple linear regressions were used to assess the association between the exposure variables and age of disease onset, assuming that a protective effect would be expressed as later age of onset. Cox proportional hazard model was used to estimate whether the dependent variables affect the rate of the progression of the disease.

Results: Smoking ≥ 10 pack years (PY) was found to be protective, delaying the age of PD symptoms onset by 3.2 years ($P < 0.05$).

At small amounts coffee or tea drinking behave as risk factors, but as consumption increased a protective effect was seen. Tea consumption exceeding 60 cup-years (CY) delayed the age of PD onset by 6.4 years ($P < 0.01$). Coffee consumption and total caffeine consumption delayed age of onset at large consumption levels, exceeding 100 CY, by 3.2 years ($P = 0.06$) and 4.2 years ($P = 0.05$), respectively. Progression of the disease, measured by the time it took patients to reach Hoehn Yahr stage III, was not affected by smoking, coffee or tea drinking.

Conclusions: Tea consumption and smoking may be associated with protection against PD by delaying its age of onset. Coffee consumption had a similar effect only at relatively large consumption levels. Tea and coffee consumption demonstrated a biphasic effect—behaving as risk factors at low doses and as protective agents at higher doses. Smoking, tea, and coffee consumption had no effect on disease progression.

P324

Does water improve gait in Parkinson's disease?

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Objective: to evaluate under water gait analysis in Parkinson's disease to use for rehabilitation strategy.

Background: Using water as the rehabilitation choice in Parkinson's disease (PD) is spurred by the following observations: under water exist two mutations of control of body position which are related to the dysfunction of the pressure receptors that in absence of bodily weight do not intervene correctly; the first one pertains to the difficulty of the body orientation in space; the second one pertains to the loss of postural reactions. Regarding rehabilitation it is interesting to note what can be the consequences of the above-mentioned difficulties of bodily orientation in space in PD that already has difficulty in controlling her own centre of gravity. This consideration is supported by studies on movement conducted in absence of gravity or of micro-gravity (such as in an aquatic environment) that have shown that in terms of physiological conditions an important compromise of the static postural regulation factor with a pronounced extension of the ankle and a backwards position of the mass centre of weight. Could a constant stimulation toward the retrograde positioning of the mass centre, as it occurs in an aquatic environment, promote new postural adaptations in PD to make the most of thereafter in gravity?

Methods: 5 inpatients with PD, average age 69.5, stage III on the Hoehn-Yahr scale, UPDRS motor section III grades between 30–40. All inpatients were evaluated by gait analysis before, under and after water during gait for 20 minutes with a digital videocamera at the same time with the same operator.

Results: Processing and analyzing data of gait analysis with Matlab system we observed an interesting improvement of gait under water in all patients; in particular we registered an augmentation of the length and of the height of the stride at constant speed, an augmentation of the upper arms' swing especially in the space behind the arms, a reduction of the stance with an augmented swing. This improvement of under water's gait is maintained after in gravity's gait. We noted that there is no freezing and a reduction of motor blocks under water.

Conclusions: This study confirms that water could be a valid rehabilitation strategy in gait improvement in PD.

P325

Six weeks intensive treadmill training improves gait and quality of life in patients with Parkinson's disease: A pilot study

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Background: Gait disturbances are common among patients with Parkinson's disease (PD), often leading to falls and functional dependence and markedly impinging on quality of life (QOL). Treadmill walking may impose a rhythm using external cueing, set the walking pace, and reinforce neuronal circuits that contribute to gait pacing.

Objective: To study whether a 6-week course of intensive and progressive treadmill training improves gait rhythmicity, functional mobility, and quality of life in patients with PD.

Methods: 9 patients with PD (mean age: 70 years) were studied before and after they participated in an intensive treadmill training program. Patients walked on the treadmill for 30 min each session, 4 training sessions per week, for 6 weeks. Once a week, usual, over-ground walking speed was re-evaluated and the treadmill speed was adjusted accordingly. QOL was assessed using the PDQ-39 (Parkinson's Disease Questionnaire). Motor performance was evaluated by measuring gait speed, stride time variability, swing time variability, the motor part of the UPDRS, the Short Physical Performance Battery (SPPB), and by using a visual analog scale (VAS) to quantify the subject's perceptions of gait and QOL. These measures have been associated with independence, fall risk, and QOL.

Results: A comparison of the measures taken before and after the treadmill intervention indicates general improvement. Parkinsonian symptoms, as measured by the UPDRS decreased (improved) from 29 to 22 ($P < 0.043$). Usual gait speed increased from 1.11 to 1.26 m/s ($P < 0.014$). Swing time variability was lower (better) in all but one patient (from 3.0% to 2.3%; $P < 0.06$) and self-assessment of gait (using VAS) improved from 6.2 to 7.5 ($P < 0.026$). Scores on the SPPB improved from 9.9 to 11.1 ($P < 0.008$). QOL as measured by the PDQ-39 was reduced (improved) from 32 to 22 ($P < 0.014$).

Conclusions: These results demonstrate the potential to enhance gait rhythmicity in patients with PD and suggest that a treadmill can be used as a powerful tool to minimize impairments in gait, reduce fall risk, and increase QOL. This rehabilitation-like program that was designed to re-train gait pacing apparently is effective in improving motor performance, gait steadiness and QOL in PD.

P326

Methylphenidate treatment improves cognitive function and gait performance in patients with Parkinson's disease

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Objective: To evaluate the effect of MPH on cognitive function, gait and fall risk in patients with PD.

Background: Among patients with Parkinson's disease (PD), gait disturbances and falls are common and a leading cause of disability and functional dependence. Cognitive disturbances are also present. In particular, executive dysfunction may exacerbate gait and fall risk in PD. We hypothesized that methylphenidate (MPH, Ritalin®) can improve cognition, especially executive function (EF) and attention, enhance gait steadiness, and reduce fall risk in patients with PD.

Design/Methods: 14 patients with PD (mean age 71 years; UPDRS motor 21.8; Hoehn Yahr Stage 2–3, Mini Mental State Exam scores 28.2) were studied before and 2 hours after administration of a single dose of MPH (20 mg). Cognitive function was tested using Mindstreams® (NeuroTrax Corp, NY), a novel web-enabled computerized neuropsychological test battery that evaluates multiple domains of cognitive function (e.g., EF, attention, memory). Gait was assessed by placing force sensitive insoles inside each subject's shoes and measuring the variability of the stride time (Coefficient of Variation—CV) during a 2-min walk and by assessing performance on the Timed Up and Go test (TUG). These two measures have been associated with fall risk.

Results: When pre and post MPH treatment performance were compared, there was a significant effect on cognitive function and gait. EF scores increased from 98.9 to 103.2 ($P < 0.015$) and attention scores increased from 103.6 to 107.2 ($P < 0.03$). Memory scores were unchanged ($P = 0.63$). There was a reduction in the stride time variability (2.2% to 1.9%, $P < 0.032$) and a significant decrease (improvement) in TUG times (12.5 to 10.8 sec, $P < 0.002$). Gait speed improved from 1.08 to 1.13 m/s ($P < 0.037$).

Conclusions: MPH (Ritalin®) treatment was associated with a differential improvement in executive function, attention, and gait performance but no improvement in memory in PD patients. This unique dual effect opens a new potential mode of intervention to decrease falls in PD. Further investigation is needed to evaluate the benefits and the long-term effects of MPH in PD.

P327

Expression of heat shock proteins in MPTP-induced mouse model of Parkinson's disease

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Objective: To investigate the expression of heat shock proteins in the mesencephalon of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine(MPTP)-induced mouse model of Parkinson's disease.

Methods: C57BL mice were chosen in the present study and randomly divided into four groups. The mice in MPTP group were treated i.p. with 5 consecutive days of MPTP (30 mg/kg/day). The mice in saline group and in sham group were given i.p. with saline and sham operation, respectively. The mice with no treatment were regarded as normal control group. The expression and localization of Hsp70, Hsp40 (including HDJ-1, and HDJ-2) and Hsp90 in mesencephalon were detected by Western blot and immunohistochemistry. The mRNA level of Hsp40 and Hsp70 was measured by in situ hybridization.

Results: Five days after MPTP injection, the expression of Hsp70, HDJ-1, HDJ-2, and Hsp90 in the substantia nigra was significantly elevated compared with normal mice as well as saline and sham groups ($P < 0.05$). These expression was gradually declined with time. Among them, Hsp70 was the most sensitive. No significant alternation was found in saline- and sham-treated groups.

Conclusion: The up-regulation of heat-shock proteins in the substantia nigra of the mouse model of Parkinson's disease may protect nigral dopaminergic neurons against MPTP.

P328

The block of ubiquitin-proteasome pathway induces cell death and the formation of ubiquitin-immunoreactive inclusions in PC12 cells

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Objective: To explore the effects of blocking the ubiquitin-proteasome pathway on cell vitality and the formation of cytoplasmic inclusions in dopaminergic cells and provide the data for elucidating the pathogenesis of Parkinson's disease.

Methods: PC12 cells were exposed to highly specific proteasomal inhibitor, lactacystin (5 μ M, 10 μ M, 15 μ M, and 20 μ M), for 24 h. The cell vitality was measured by MTT assay. The expression of high molecular weight ubiquitinated proteins was analyzed by Western Blot. The formation of ubiquitin immunoreactive inclusions was determined with immunofluorescence cytochemistry staining.

Results: After exposed to lactacystin (5 μ M, 10 μ M, 15 μ M, and 20 μ M) for 24 h, PC12 cells showed a dose-dependent decrease in cell vitality. Western Blot confirmed that no high molecular weight ubiquitinated proteins were found in control cells and an obvious dose-dependent accumulation of high molecular weight ubiquitinated proteins was detected in cells treated with lactacystin. Immunofluorescence staining showed that low-level diffuse ubiquitin immunoreactivity was displayed in control cells and ubiquitin immunoreactive inclusions were only found in very few control cells. In PC12 cells treated with 20 μ M lactacystin for 24 h, the number of cells including cytoplasmic ubiquitin immunoreactive inclusions increased significantly ($P < 0.01$).

Conclusions: The dysfunction of ubiquitin-proteasome pathway could induce cell death, cause the accumulation of ubiquitinated proteins and promote the formation of cytoplasmic ubiquitin immunoreactive inclusions in dopaminergic cells, which may contribute to degeneration of dopaminergic neurons and Lewy body formation in substantia nigra of patients with Parkinson's disease.

P329

Auditory event-related potentials in Parkinson's disease in relation to memory function: A 10-year follow-up study

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Objectives: The purpose of the study was the longitudinal evaluation of Auditory Event-Related Potentials (AERPs) in patients with Parkinson's disease (PD) in relation to memory function. Background: AERPs, particularly the P300 component, have been found abnormal in patients with PD. This abnormality has been related to various aspects of cognitive function, but its exact relation to disease progression and cognitive decline remains controversial.

Method: Twenty-two non-demented PD patients entered the study. AERPs were assessed at baseline and 10 years later by means of the standard "odd-ball" paradigm. Their memory function was evaluated by means of the Wechsler Memory Scale (WMS). At baseline 30 matched for age normal subjects were assessed by AERPs and served as controls.

Results: At baseline P300 latency in PD patients was significantly prolonged compared to controls ($P 0.001$). This prolongation correlated negatively to WMS visual reproduction score ($P 0.005$). Ten years later P300 latency remained unchanged in PD patients. However, WMS digit span and visual reproduction scores deteriorated ($P 0.023$ and $P 0.004$, respectively). A negative correlation was found between P300 latency at ten years and WMS visual reproduction ($P 0.02$) as well as WMS logical memory scores ($P 0.03$).

Conclusions: Our findings indicate that although P300 latency is prolonged in PD patients it does not reflect disease progression. An association between P300 abnormality and memory function remains unchanged over time.

P330

Postural instability evaluation in Parkinson's disease patients

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Background: Postural instability is one of the most incapacitating factors in Parkinson's disease (PD) that often leads to falls. This problem becomes accentuated with the progression of the disease.

Aim: To verify a diagnostic value of posturography in evaluation of postural instability in PD patients by measuring sway during quiet stance.

Material and Methods: We examined 55 PD patients (35 males, in mean age 64.6 years, scoring 1-3 stage according to Hoehn Yahr Staging). They all did not exhibit any dyskinesias or fluctuations and were tested in ON phase. The control, age-matched, group consisted of 55 healthy subjects. Our test consisted of two trials: with eyes open (EO) and eyes closed (EC). Sway path length (SPL), sway ranges: antero-posterior (Srap) and medio-lateral (SRml) were measured on force platform (QFP Medicapteurs, France). Data were analyzed using 2×2 ANOVA and Spearman's correlation test.

Results: SPL is the most relevant parameter for postural control evaluation. The mean SPL increased from 470.84 ± 299.49 mm in EO to 686.21 ± 411.95 in EC conditions in our PD patients. Controls exhibited significantly shorter path length 312.71 ± 124.28 mm in EO and 433.8 ± 172.55 in EC conditions. ANOVA showed significant effect of the group [$F(1,108) = 16.97, P < 0.000075$] and vision [$F(1,108) = 98.95, P < 0.0000$]. Sway ranges in both planes were lower in the control group and in both groups increased in EC. The mean Srap value in PD patients was 26.72 ± 9.72 mm (EO) and 33.92 ± 15.5 (EC) while in the control group 21 ± 7.35 mm (EO) and 28.26 ± 10.05 (EC). Both differences were statistically significant. Similarly, the highly significant changes in the

SRml were documented ($EO 14.81 \pm 5.38$ mm and 20.29 ± 13.3 in PD and control, respectively, and increased in EC to 15.39 ± 6.57 mm (control) and 26.39 ± 16.7 mm (PD). The SRml strongly correlated with the stage of the disease.

Conclusions: Gradual increase of postural instability with progress of PD could be documented. In contrast to the normal subjects, PD patients seem to depend more on vision in control of posture. Majority of sway parameters did not correlate with patients' age, which is probably due to other PD motor symptoms and pharmacological treatment; thus, posturography cannot be applied directly for evaluation of the PD stage.

P331

Efficacy and safety of weak electromagnetic fields in Parkinson's disease patients

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Background: An idea of effect of external magnetic fields is based on that appropriate external stimuli can result in the mobilisation of regenerative processes. Magnetic fields improve the interneuron conductivity and modulation of neuron activity. It can be assumed that transcranial application of weak electromagnetic fields can help to restore a functional equilibrium in dopaminergic pathway.

Aim: To assess the therapeutic effect of transcranial application of weak electromagnetic fields with Viofor JPS in PD patients.

Materials and methods: 40 patients, aged 30–80, diagnosed with idiopathic PD, scoring 1–3 stage in Hoehn Yahr Staging were included into the study. 22 PD patients had motor fluctuations and/or dyskinesias. The control group consisted of 18 PD patients free of motor fluctuations and/or dyskinesias. All PD patients were randomized into treatment or placebo group. The weak electromagnetic fields were generated utilizing ionic cyclotron resonance with constant intensity and were applied with Viofor JPS (MedLife, Poland). The magnetic treatment was applied daily during 14 days. Clinical assessment was done by neurologists specialized in movement disorders who was blinded to randomization. It consisted of Modified Hoehn Yahr Staging, Unified Parkinson's Disease Rating Scale (UPDRS), Goetz Dyskinesia Scale, and Clinical Global Impression Scale. All PD patients noted the duration of ON and OFF time in the diary and they all underwent close medical and laboratory safety analysis.

Results: There was no effect of magnetic fields on motor complications in PD patients. The duration of ON/OFF time, the presence and the intensity of dyskinesias were not changed during the study. The progression of the PD according to UPDRS III was higher in PD patients with dyskinesias in the placebo group than in the treatment group ($P < 0.05$). No side effects accompanied to the magnetic treatment were observed.

Conclusion: Transcranial application of weak electromagnetic fields was a safe procedure with no effect on motor complications in PD. It is possible that weak electromagnetic fields can reduce the progression of parkinsonian symptoms, which need to be confirmed in further studies.

P332

Pain in Parkinson's disease

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Objective and Background: Pain is reported by nearly half of patients with Parkinson's disease (PD). In some patients, it can be severe or intractable and more distressing than the motor symptoms. There have been few studies assessing the frequency and nature of pain in PD. We assessed the prevalence of pain and potential underlying causes in patients with PD.

Methods: A total of 96 patients with PD (42 female, 54 men) participated. The mean age was 62.3 ± 11.7 (25–84) years and the mean duration of illness was 5.5 ± 4.2 (1–24) years. UPDRS, Hoehn-Yahr, Leeds pain scale, anxiety scales (STAI- TX 1 and 2) were administered to all patients. Depression was assessed with geriatric depression scale and Beck's depression scale.

Results: Pain as the first symptom of PD was seen in 3 (2.8%) of patients. 63 (64.9%) out of 96 patients with PD, reported pain. Pain types included the musculoskeletal type of different etiologies (osteoarthritis,

frozen shoulder, rotator cuff rupture, scoliosis, abnormalities of posture, post-traumatic): 25 patients (39.7%), radicular or neuropathic pain: 6 patients (9.5%), pain secondary to dystonia: 12 patients (19%), central pain: 7 patients (11.1%), and unclassified type: 5 patients (7.9%); 8 patients (12.7%) described more than one type of pain. Pain did not correlate with sex, duration of disease, depression, anxiety, sleep disturbances, fatigue, age at onset of PD or history of disease in first-degree relatives. Akathisia seemed to be correlated with presence of pain ($P < 0.02$).

Conclusions: Our results suggest that pain is one of the most common non-motor symptoms in patients with PD. In order to identify the appropriate treatment strategy, it is essential to identify the underlying etiology.

P333

Sialorrhea: Validation of a method for objective measurement and a clinical scale in Parkinson's disease patients

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Background Objective: at least 70% of Idiopathic Parkinson's Disease (IPD) patients complain about sialorrhea. The objective of this study was to validate a new instrument for the measurement of the content of saliva in the mouth and for the evaluation of patient subjective perception of excessive saliva secretion by means of a clinical scale.

Methods: Pooling of saliva in the mouth was measured by placing dental cotton rolls under the tongue, and subjective perception was classified according to a score provided by a 7-item retrospective self-administered survey (range: 0 to 21 points). The study was divided in three phases.

Phase 1: The content of saliva in the mouth was measured in 19 healthy young volunteers twice, 7 days apart. Intra- and interobserver agreement was checked with Spearman's correlation.

Phase 2: The survey was given to 39 IPD patients. Reliability of the survey was checked by employing Chronbach test.

Phase 3: The content of saliva in the mouth was measured and the survey was given to 47 additional IPD patients.

Results: The relationship between pooling of saliva, perception, and characteristics of the patients was analyzed. The correlation between salivation in the healthy subjects measured on the two occasions was 0.83 ($P < 0.001$). When the measurements were performed by the same person the correlation was 0.90; however, when it was performed by a different investigator the correlation changed to 0.81. Standardized Cronbach alfa, a measure of reliability was 0.78 (a value between 0.7 and 0.8 is acceptable). Average inter-item correlation was 0.35. Of the 47 patients recruited for the last phase, 62% complained of sialorrhea. The subjective score for these patients correlated significantly with the content of saliva in the mouth ($r = 0.42$, $P = 0.03$). Patients without sialorrhea complaints had a lower subjective score and less salivation, but only the subjective score difference was statistically significant.

Conclusion: Our method for measuring the content of saliva in the mouth and subjective perception of sialorrhea was reasonably reliable and showed excellent intra- and interobserver agreement. The use of validated methods is critical for the appropriate evaluation of current and future therapeutical interventions for sialorrhea.

P334

Handwriting graphometric analysis in idiopathic Parkinson's disease and parkinsonism

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Background: Micrographia is a well-known feature of Idiopathic Parkinson's disease (IPD). Diminished amplitude and velocity of stroke have been described in Secondary Parkinsonism (SP); but whether this impairment is different from that found in IPD is unclear.

Objective: To assess handwriting characteristics in IPD patients, and compare them with those found in SP. To analyze the evolution of handwriting impairment in terms of disease stage, and search for differences in writing when IPD patients were evaluated in ON vs. OFF state.

Methods: Thirty-six patients with IPD and 10 with SP prospectively recruited from our outpatient movement disorders clinic were asked to copy a sentence and to draw lines, circles, and boxes on a blank sheet of paper. Handwriting samples were evaluated for the presence or absence of 15 graphological characteristics by a handwriting expert chosen in advance, blind to clinical diagnosis.

Results: IPD patients with micrographia presented higher UPDRS and HY score than patients without micrographia ($P = 0.03$ for both, Mann-Whitney). No differences were found when patients were evaluated in ON vs. OFF state regarding any of the studied characteristics. Base line not fitting the row and exceeding it were more frequent in SP than in IPD ($P = 0.02$ and $P = 0.01$ respectively, Fisher test).

Conclusion: Our results suggest that handwriting characteristics depend on the severity of disease, and result from an alteration of dopaminergic as well as non-dopaminergic pathways. The relationship between handwriting base line and row line, which is easily evaluated in the physician's office, is the only parameter that could suggest parkinsonian symptoms of secondary origin.

P335

Clinical correlates of levodopa-induced increases in brain dopamine levels in Parkinson's disease: An ^{11}C -raclopride PET study

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Objective: To correlate individual changes in motor performances of patients with advanced Parkinson's disease (PD) with increases in synaptic dopamine (DA) levels induced by a single oral dose of levodopa (LD) measured in vivo by ^{11}C -raclopride (RAC) PET.

Background: RAC PET provides an in vivo measure of synaptic DA levels as evidenced by changes in D2 receptor availability. A recent PET study has shown that striatal reductions in RAC binding after a fixed dose of LD become larger with PD progression. These increasing synaptic DA responses to LD as the disease progresses may be responsible for the emergence of dyskinesias. To date, no study correlating LD-induced synaptic DA increases with motor response in PD patients has been reported.

Methods: 16 patients with advanced PD (disease duration 11.9 ± 5.4 years, mean \pm SD; UPDRS motor score 44.9 ± 18.7) were studied. Each patient was assessed with RAC PET twice: without and after an oral 250mg LD challenge. UPDRS motor score were performed in "off" and at the end of the LD scan.

Results: All the patients were still "on" at the end of the LD scan. Following LD, RAC Binding Potentials (BP) for caudate and putamen were significantly lower compared to baseline by 9% and 12%, respectively. Individual % changes in UPDRS from "off" to "on" after LD significantly correlated with individual putamen increases in DA levels ($P < 0.01$). Putamen increases in DA and UPDRS improvements did not correlate with either disease duration or with UPDRS in "off."

Examining UPDRS sub-items, improvements in rigidity and bradykinesia, but not in tremor, correlated positively with putamen DA increases ($P < 0.01$; $P < 0.03$; $P = 0.43$). Additionally, greater putamen DA increases after LD correlated with higher dyskinesias scores ($P = 0.01$).

Conclusions: In advanced PD patients the magnitude of improvement of rigidity and bradykinesia after a single dose of oral LD correlates with the induced DA increases in striatal synaptic clefts, but is independent of baseline disease severity when "off" and disease duration. Dyskinesia severity is also significantly correlated with the amount of exogenous DA generated from LD. In contrast, the response of PD tremor to LD does not appear to be related to putamen DA levels.

P336

Entacapone increases and prolongs the central effects of levodopa in the 6-hydroxydopamine-lesioned rat

M. Gerlach, M. van den Buuse, C. Blaha, D. Bremen, P. Riederer (Wurzburg, Germany; Parkville, Victoria, Australia; Sydney, Australia; Hamburg, Germany; Wurzburg, Germany)

Objective: To investigate the effect of adding the COMT inhibitor entacapone to chronic treatment with levodopa and the peripherally active AADC inhibitor benserazide.

Background: Strategies designed to prolong and smooth the delivery of levodopa to the brain might decrease the tendency of levodopa to induce pulsatile stimulation of striatal dopamine receptors and reduce the risk of motor complications in PD patients. These strategies include the use of a COMT inhibitor such as entacapone which, when used concomitantly with levodopa and an AADC inhibitor, has been shown to increase the duration of the clinical response to levodopa. This pharmacotherapeutic approach may also reduce dyskinesia induction and allow a reduction in levodopa dosage.

Methods: Male Sprague-Dawley rats ($n = 40$) with a unilateral 6-hydroxydopamine induced lesion were divided into 5 experimental groups; 1 group was treated 2 \times daily with levodopa (6.5 mg/kg) and benserazide (1.5 mg/kg i.p.) for 2 weeks and the remaining groups were treated 2 \times daily with entacapone (10 mg/kg i.p.) and levodopa (1.5–6.5 mg/kg i.p.). At 16–18 days following treatment, striatal extracellular dopamine levels were determined in the lesioned unlesioned striata by chronoamperometry.

Results: Animals receiving entacapone in addition to 6.5 mg/kg of levodopa/benserazide displayed significant enhancement of the developing contralateral turning response compared to rats treated with the same dose of levodopa alone. Animals receiving entacapone in addition to a lower dose of 4.25 mg/kg of levodopa/benserazide exhibited a behavioural response comparable to that seen in rats treated with the higher 6.5 mg/kg dose of levodopa alone. Voltammetry analysis suggested that the increased behavioural response in entacapone-treated animals was due to a much larger dopamine release. In addition, it was found that entacapone treatment prolonged smoothed striatal dopamine levels following chronic levodopa/benserazide treatment.

Conclusions: This finding suggests that, with concomitant COMT inhibition, PD patients with fluctuations can have their motor function improved with a reduced risk of experiencing dyskinesias vs. higher doses of traditional levodopa. In addition, the smoother delivery of levodopa to the brain is theorized to reduce the risk of dyskinesia induction.

P337

Admission of parkinsonian patients to the neurological ward in a community hospital: A 6.5 years screening

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Objective: To analyze the reasons for admission of Parkinsonian patients to a neurological ward in a community hospital and the outcome of the hospitalization.

Background: Parkinson's disease patients (PD pts) chronically treated with levodopa (LD) are frequently admitted to hospital due to disease or treatment-related complications, with its related burden to the health system. The aim of this study was to analyze which factors influence hospitalization.

Methods: From 1/1/98 to 1/9/04, 1,920 patients (aged 50 years and over) were admitted to our Department, among them 143 (7.5%) with PD as the main diagnosis. The PD population included 88 males and 55 females; mean age 69.5 years \pm 6; mean disease duration 9.2 years \pm 6.4; and 58 (41%) were demented. *Statistics:* *t*-test, one-way ANOVA, Pearson correlation, and Tukey's method for multiple comparisons were applied for analysis of data, which included age; sex; staging of PD; disease duration; motor disturbances (falls, offs, dyskinesias); mental complications (dementia, depression, psychosis, delirium); somatic problems; or a combination of these.

Results: One hundred forty-three PD pts were hospitalized 243 times (104 pts 1 admission and 39 pts 139 admissions). Mean duration of hospitalization of PD pts was 11.1 ± 6.3 days; mean hospitalization duration of other patients in the ward (over 50 years) was 7.1 ± 4.9 days. The main reasons for admission of PD pts were motor complications (37%), which required shorter hospital stays (9 ± 4.6 days). Factors that significantly influenced duration of hospitalization ($n = 143$) were age, staging, dementia, and the presence of delirium, the last being the most significant ($P = 0.002$). Recurrent admissions ($n = 39$) were more commonly observed in pts with longer disease duration ($P = 0.002$). Also, delirium ($P = 0.005$), motor complications (frequent offs) ($P = 0.03$), and somatic disorders ($P = 0.06$) played a role in repeated admissions.

Conclusions: Delirium seems to be the strongest factor influencing the number and length of hospitalizations. We believe that adequate information to the caregivers and better control of the general condition of the PD pts, with close monitoring of their treatment, may diminish hospital admissions with its associated medical, social and economic benefits.

P338

Deep brain stimulation improves temporal discrimination in Parkinson's disease

I.D. Zamarbide, F. Alonso-Frech, M.C. Rodriguez-Oroz, J. Guridi, M.A. Pastor, J. Artieda, et al. (Pamplona)

Objective: To study the effect of bilateral deep brain stimulation (DBS) of the subthalamic nucleus (STN) or globus pallidus pars interna (GPI) on somesthetic temporal discrimination thresholds (STDT) in patients with Parkinson's disease (PD).

Background: Large current evidence indicates that dopaminergic neurotransmission in the basal ganglia plays an important role in temporal processing. Several studies have shown an impairment of different timing tasks in PD that could be attenuated by dopaminergic therapy. Temporal discrimination thresholds (TDT) for recognition of paired sensory (somesthetic, auditory and visual) stimuli have demonstrated to be an easy and reliable test for time estimation.

Patients and Methods: STDT were studied in the following groups: 1) Fifteen patients with PD submitted to bilateral DBS (11 STN, 4 GPI), 2) Seven patients with PD treated with standard medication, 3) 10 age-matched normal subjects. Assessments were performed "OFF medication" after an overnight withdrawal of antiparkinsonian drugs for all patients and DBS "ON" and "OFF" condition in the surgical group.

Results: STDT was significantly increased in all PD population (pharmacologically treated and surgical group) compared with controls.

PD population pharmacologically treated showed significantly higher values (mean 134.2 ± 25 ms) vs. normal subjects (mean 31.7 ± 12 ms).

There was a significant improvement in STDT when the stimulation was turned "ON" (mean 64.3 ± 31 ms) compared with stimulation "OFF" (mean 85.3 ± 40 ms) ($P < 0.001$).

Conclusion: DBS of the STN and GPI improves TD in PD patients. These results confirm a specific role of the basal ganglia and its thalamocortical connections in temporal information processing.

P339

Parkinson's disease patient survey: Managing unexpected off episodes

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Objective: To determine (1) the characteristics of off episodes, (2) predictors of unexpected wearing off of medication, and (3) the impact of unpredictable off episodes on patients with Parkinson's disease (PD)

Background: PD patients may be able to avoid off episodes if they can sense it coming before the next dose.

Methods: A 16-item questionnaire was developed to collect self-report information from PD patients. The questionnaires were distributed in neurologists' offices asking for anonymous response and return by mail. Correlation analyses and logistic regressions were performed.

Results: Responses were received from 727 patients, mean age 63.6 ± 12.9 years, 59% male, 6.3 ± 6.1 years taking PD medications, 80% living at home without skilled assistance, and 63% walking independently. The median frequency of off episodes was 14/week, with most patients having approximately 3 occurring an hour before, and 1 occurring an hour after taking a dose of medication. Thirty-nine percent of patients often/always could predict when their medication would wear off, with 72% having some warning so they could take medication. A third of patients reported depression and anxiety about off episodes. Off episodes were a moderate/major bother to 55% of patients, particularly limiting a job (44%), driving (33%), social activities (31%), physical activities (30%), and working at home (29%).

A multiple regression model derived a profile of patients who were able to predict when their medication would wear off. The predictors included frequency of episodes, suddenness of episodes, depression/anxiety, home status, and level of independent activity (overall $R^2 = 0.20$, $P < 0.001$). The strongest predictors were frequency and suddenness (R^2 0.05, 0.024, respectively, both $P < 0.01$). Another regression derived a profile of patients who were more affected by depression/anxiety related to episodes. The same variables showed a significant overall effect ($R^2 = 0.39$, $P < 0.001$). The strongest predictor was suddenness ($R^2 = 0.105$, $P < 0.01$).

Conclusions: These data define a large subgroup of PD patients who often can predict when their medication will wear off, and have adequate time to plan. These patients might benefit from availability of a rescue therapy to treat off episodes.

P340

Entacapone but not folate prevents L-dopa-induced hyperhomocysteinemia

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Objective: We studied whether a co-treatment with entacapone or folate prevents levodopa induced hyperhomocysteinemia.

Background: Treatment with levodopa for Parkinson's disease (PD) increases total homocysteine (tHcy) plasma level by activating the catechol-O-methyltransferase (COMT)-mediated methylation metabolism. Hyperhomocysteinemia, however, is a risk factor for arteriosclerotic vascular events and possible for dementia.

Methods: A total of 27 Wistar rats were randomly treated with levodopa or levodopa plus entacapone or levodopa plus folate. tHcy was measured at baseline, 4 h, 8 h, and 12 h after treatment.

Results: Treatment with levodopa caused a threefold increase of tHcy 4 h after application. Co-treatment with folate had no effect on the resulting tHcy plasma level. Entacapone inhibited the increase of tHcy effectively and shifted tHcy-peak levels to 8 h after treatment.

Conclusion: To reduce the secondary risk of coronary heart disease and stroke, tHcy should be controlled in patients receiving levodopa by early co-treatment with COMT-inhibitors.

P341

Excessive daytime sleepiness and the future risk of Parkinson's disease

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Objective: To determine if excessive daytime sleepiness (EDS) can predict future Parkinson's disease (PD) in the absence of prevalent PD and confounding due to treatment for PD.

Background: While EDS is common in PD, it remains equivocal if EDS is related to the neuropathologic processes leading to PD, is a consequence of PD, or is secondary to the treatment of PD. There are no prospective follow-up studies for PD in the presence versus the absence of EDS, and it is not known if EDS can predate PD.

Methods: EDS was assessed in 3079 men aged 71 to 93 years in the Honolulu-Asia Aging Study from 1991 to 1993. All were without PD and dementia. Follow-up for incident PD was based on neurologic examinations that occurred from 1994 to 1999.

Results: During the course of follow-up, 24 men developed PD (16.6/10,000 person-years). After adjusting for age, there was a significant 4-fold excess in the risk of PD in men with EDS versus men without EDS (54.3 vs. 13.5/10,000 person-years; relative odds [RO], 4.1; 95% confidence interval [CI], 1.3–10.9; $P = 0.02$). Additional adjustment for insomnia, cognitive function, depressed mood, mid-life cigarette smoking and coffee drinking, and other factors failed to alter the association between EDS and PD (RO, 3.9; 95% CI, 1.1–10.6; $P = 0.02$).

Conclusions: Findings suggest that EDS is associated with an increased risk of future PD. Observations provide support for the argument that the relation between EDS and progression to clinical PD is closely linked with neurodegeneration in PD.

TABLE 1. Abstract 342: PLM/h of TST at baseline and after each single dose treatments

PSG variable	Treatment					
	Baseline (N = 28)	LCE 50 (N = 28)	LCE 100 (N = 28)	LCE 150 (N = 27)	LC (N = 28)	Placebo (N = 28)
Mean PLM/h TST (SD)	23.7 (17.3)	12.6 (12.0)	6.4 (8.6)	3.5 (6.0)	9.5 (14.8)	25.7 (24.8)

P342**Levodopa optimized with entacapone decreases periodic limb movements in patients with restless legs syndrome**

O. Polo, R. Ylä-Sahra, K. Hirvonen, J. Karvinen, M. Vahteristo, J. Ellmén (Turku, Finland)

Objective: The aim of this study was to investigate objective sleep measures in patients with restless legs syndrome (RLS) after treatment with single doses of levodopa/carbidopa/entacapone (Stalevo®) tablets, traditional levodopa/carbidopa (LC), or placebo. 80% of RLS patients have frequent periodic limb movements (PLM) during sleep, and this PLM frequency correlates with other symptoms of RLS. PLM and other sleep variables were measured by polysomnography (PSG).

Method: This was a randomized, double-blind, placebo-controlled, single-dose, cross-over study. Patients were randomized to receive one tablet of Stalevo 50 (levodopa 50 mg/carbidopa 12.5 mg/entacapone 200 mg), Stalevo 100 (100/25/200), Stalevo 150 (150/37.5/200), LC 100 (100/25) or placebo, for 5 consecutive periods. There was a 4–8 day wash-out between the periods. The primary efficacy measure was PLM/h TST (Total Sleep Time), recorded twice during screening and once during each subsequent period. Secondary variables included PLM/h for the first and second half of the night during time in bed (TIB).

Results: 28 subjects, 10 men and 18 women, mean age of 51.2 years (27–68 years), were included. Mean PLM/h TST was significantly better with all doses of Stalevo compared with placebo ($P < 0.001$ for Stalevo 100, Stalevo 150 and LC 100, $P = 0.0212$ for Stalevo 50) (Table 1). The general pattern for secondary efficacy variables was (in order of decreasing potency): Stalevo 150 > Stalevo 100 > LC 100 > Stalevo 50 > placebo and baseline. In the last 4 h of the night, Stalevo 100 had significantly better efficacy compared to LC 100 ($P = 0.01$). Adverse event incidence was low and similar among treatment periods.

Conclusions: Single doses of Stalevo 50, 100, and 150 were all significantly superior to placebo in reducing the number of PLM during the total sleep time in patients with RLS.

There was a dose-related effect of Stalevo on PLM per hour.

Stalevo 100 had prolonged activity compared with LC 100 during the second half of the night (Table).

P343**Prevalence of bladder dysfunction in Parkinson's disease**

K. Winge, H. Stimpel, K.K. Nielsen, L. (Werdelin Denmark)

Background: Patients with Parkinson's disease (PD) often have lower urinary tract symptoms (LUTS). In the studies most recently published on PD patients diagnosed according to published criteria, the prevalence of urinary symptoms is 27%–39% based on validated questionnaires.

Aim: To evaluate the prevalence of LUTS in patients with PD, the severity of symptoms and the volume of postmicturitional urine (PMV).

Methods: Patients with Parkinson's disease were interviewed using 2 sets of questionnaires regarding LUTS; the International prostate symptom score *IPSS*, and the Danish prostate symptoms score, *Dan-PSS*. *Dan-PSS* has an integrated score addressing bothersomeness of symptoms where as *IPSS* addresses the prevalence and severity of symptoms. Severity of disease was assessed by the modified Hoehn Yahr rating scale. Volumes of postmicturitional urine were measured using BladderScan™ ultrasound equipment.

Results: 107 patients were evaluated. *DanPSS*-scores correlated significant with Hoehn Yahr stage of disease ($P = 0.02$), but not with duration of disease or age. *IPSS*-scores did not correlate to stage of disease, duration of disease or age. Two arbitrary cutoffs were applied, identifying patients

with significant LUTS, *Dan-PSS* > 10 and *IPSS* > 10. There were no significant differences between the age or duration of disease of patients with and without significant LUTS. Patients with significant bothersome LUTS (*Dan-PSS* > 10), belonged to a significant higher stage of disease than patients who scored <10 on *Dan-PSS* (2.2 vs. 2.0, $P = 0.05$).

The most frequent symptom was nocturia (*IPSS*: 86%) followed by frequency (*IPSS*: 71%) and urgency (*IPSS*: 68%). The most frequent reported troublesome bladder symptom (*Dan-PSS*) was urgency (61%), followed by nocturia (50%) and urge incontinence (44%).

Mean PMV was 34 mL. Seven patients (6%) with PD had a PMV larger than 100 mL. The PMV did not correlate to stage of disease or to scores on questionnaires.

Discussion: Prevalence of severe LUTS are in line with other studies, but the correlation between *Dan-PSS* and Stage of disease, but not *IPSS* indicates that though we see no increase in frequency and severity of LUTS as PD progresses, patients find symptoms more troublesome. This may be due progression in gait difficulties, or a result of a decreasing ability separate and integrate sensory input.

P344**Seletracetam (UCB 44212) reduces L-dopa-induced dyskinesia in the MPTP-lesioned marmoset model of Parkinson's disease**

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Introduction: Seletracetam (ucb 44212) is a new pyrrolidone derivative of levetiracetam (Keppra), with potent activity and high tolerability in animal models of epilepsy. Recent studies have shown that Keppra reduces L-dopa-induced dyskinesia in MPTP-lesioned marmoset and macaque models of Parkinson's disease. Thus, the current study was designed to assess the ability of seletracetam to reduce dyskinesia following L-dopa monotherapy in the MPTP-lesioned marmoset model of Parkinson's disease.

Methods: Nine marmosets were rendered parkinsonian by administration of MPTP. L-dopa-induced dyskinesia was induced by prior treatment with L-dopa, twice daily for 21 days. Following this priming process, all animals displayed reproducible "marked" dyskinesia when challenged acutely with L-dopa (12 mg/kg). The effect of oral administration of seletracetam (1, 3, 10, and 30 mg/kg), when given in combination with L-dopa (13.9 ± 0.8 mg/kg), were assessed.

Results: At all four doses of seletracetam, L-d/seletracetam combination therapy elicited an equivalent anti-parkinsonian effect to L-dopa monotherapy. Administration of seletracetam at 10 mg/kg and 30 mg/kg in combination with L-dopa resulted in significantly less dyskinesia than L-dopa monotherapy.

Discussion: This study suggests that seletracetam may reduce dyskinesia induced by dopamine replacement therapies without affecting their anti-parkinsonian efficacy. In addition, these data further support the potential of this class of drugs in the treatment of dyskinetic side-effects of dopamine-replacement therapies.

PARKINSONISM—OTHER**P345****The basal ganglia cholinergic neurochemistry of progressive supranuclear palsy**

N.M. Warren, M.A. Piggott, D.J. Burn (Newcastle upon Tyne, United Kingdom)

Objective: To measure muscarinic M2 and M4 receptors in the striatum and pallidum of patients with progressive supranuclear palsy (PSP).

Background: PSP is a progressive neurodegenerative disorder with motor and cognitive dysfunction, and a pathological predilection for subcortical structures, including the substantia nigra, globus pallidus, and subthalamic nucleus. There is no effective treatment either for symptomatic relief or disease modification. This relates in part to a lack of knowledge of the underlying neurochemical abnormalities, particularly cholinergic receptor status in the striatum.

Method: We measured, autoradiographically, muscarinic M2 (presynaptic), and M4 (postsynaptic) receptors in the anterior and posterior striatum and pallidum of pathologically confirmed cases of PSP (total n = 17, 16 anterior, 11 posterior), and controls (total n = 52, 38 anterior, 22 posterior). M2 receptors were visualised with 4.8 nM [³H]AF-DX 385 in the presence of 10 nM dicyclomine, and M4 measured by subtraction of M2 density from combined M2/M4 binding (AF-DX in the absence of dicyclomine).

Results: In both PSP and control groups M2 and M4 binding was highest in the caudate, putamen and nucleus accumbens. There was markedly less binding in the pallidum. In PSP, there was a reduction in M2 and M4 receptors in the posterior caudate ($P < 0.01$ for both receptors) and a reduction in M2 receptors in the posterior putamen compared to controls ($P < 0.01$). M4 receptors were elevated in PSP in the internal globus pallidus (GPi) ($P < 0.01$).

Conclusions: The reduction in posterior striatal M2 receptors in PSP cases is most likely due to loss of cholinergic interneurons. The reduction of posterior caudate M4 receptors suggests loss of medium spiny projection neurons bearing these receptors, which may be neurons of the direct pathway, also expressing D1 receptors. Knowledge of receptor status in PSP may lead to a greater understanding of neuronal selective vulnerability to the disease process and also refine targeting of cholinomimetic therapeutic agents. Further work is needed to compare these results in PSP to neurodegenerative diseases with similar symptomatology.

P346

Adult Westphal variant of Huntington's disease: A video presentation *S. Kamath, N. Bajaj (Derby, Derbyshire, United Kingdom)*

Objective: Illustration of heterogeneity in adult Huntington's disease (HD) with parkinsonism, cognitive impairment, and no chorea.

Background: Classic adult presentation of HD is with chorea and cognitive impairment. Parkinsonian presentations are commonly seen in the juvenile Westphal variant (onset before 20 years old),¹ but are rarely reported in adults. We believe this to be the first video presentation of such a case.

Methods: Clinical evaluation with video presentation of a single case history. HD was confirmed genetically.

Results: We present a 36-year-old man who initially developed poor short term memory and dysarthria. There was no history of involuntary movements. There was a family history of HD.

On examination eye movements showed saccadic intrusion on smooth pursuit and saccades were hypometric. There was impersistence of tongue protrusion. Gait was abnormal with stooped posture and reduction of bilateral arm swing. There was axial rigidity. Postural reflexes were impaired. There was mild bilateral bradykinesia and reduction in amplitude of arm movements without chorea. Minimal state examination score was 27/30 with 2 points lost for 3 object recall and 1 for orientation.

CT brain showed caudate atrophy and a genetic screen for HD was positive.

Apomorphine challenge testing failed to show any improvement and was poorly tolerated. There was no unmasking of chorea.

Conclusions: The parkinsonian predominant presentation in HD is recognised in adolescents as the Westphal variant. This presentation has rarely been reported in adult patients.² We present the first video of such a patient and demonstrate the lack of chorea, more than 2 years into the illness, despite provocation with apomorphine. Unlike previous case reports, our patient did not show a levodopa response. We suggest the term Adult Westphal variant for these parkinsonian dominant/chorea-negative adult HD patients.

References

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P347

Heterogeneity of vascular parkinsonism: Clinical-MRI correlates *O.S. Levin, N.A. Unischenko, D.Y. Olunin (Moscow, Russia)*

Objective: To reveal MRI findings specifically associated with VP.

Background: Vascular parkinsonism (VP) is a syndrome caused by ischemic or hemorrhagic lesions of different segments (frontostriatal, striatopallidal, nigrostriatal, or thalamofrontal) of motor cortico-subcortical circuit. VP frequently associates with small vessels disease and manifests as bilateral akinetic-rigid syndrome with early prominent gait disorders, postural instability, and variable response to L-dopa.

Methods: Twenty-three patients with clinically probable VP (mean age 67.8 ± 5.6 years) and 29 age-matched hypertensive patients with chronic cerebrovascular insufficiency without parkinsonian signs were studied. Probable VP was defined as parkinsonism (hypokinesia plus rigidity and/or resting tremor) with evidence of cerebrovascular lesions on MRI associated with 1) atypical for Parkinson's disease or parkinsonism plus syndromes clinical features, and/or 2) clinical evolution with acute/subacute onset (6 or less months after stroke) or stepwise course.¹ The severity of parkinsonian signs was measured with Part III of the Unified Parkinson's Disease Rating Scale (UPDRS). MRI of the brain was performed with "Magnetom-SP 63" (1.5T) scan. There were not significant differences in MMSE and other neuropsychological tests performances between two groups.

Results: Multiple lacunae in subcortical gray and white matter and/or diffuse white matter lesions (leukoaraiosis) with enlargement of lateral ventricles were found in patients of both groups. There were not significant differences in average number of lacunae or total area of periventricular and subcortical leukoaraiosis between two groups. But patients with VP had significantly more lacunae in putamen and globus pallidus, than patients without VP ($P < 0.05$). The former were also tended to have more extensive frontal leukoaraiosis ($P = 0.09$) and more large lateral ventricles than latter ($P = 0.07$). There was not correlation between UPDRS score and MRI data. But the severity of rigidity is positively correlated with putaminal lesions and the severity of postural instability and gait disorder are correlated with pallidal lesions and lateral ventricles area ($P < 0.05$).

Conclusion: VP may be associated with strategically located lesions involving putamen, globus pallidus or specific white-matter pathways.

Reference

1. Levin, 1997.

P348

Frequency of vascular parkinsonism: A follow-up study of 1.964 patients from a specialized clinic

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Objective: To assess the frequency of vascular parkinsonism (VP) at follow-up among a large group of parkinsonian patients seen in a hospital-based specialized clinic in the Spanish Health System.

Background: Although a vascular cause is often entertained in patients with secondary parkinsonism, the real frequency of VP is largely unknown.

Methods: We analysed the outcome of 94 patients included in a database as possible VP out of 1.964 patients with parkinsonism seen along 14 years. Patients are usually referred by general neurologists from a catchments area of 635,000 people. VP was defined in the presence of at least 2 out of 3 cardinal signs in the limbs plus neuroimaging evidence of bilateral ischaemic damage deep in the cerebral hemispheres, and no evidence of a better alternative diagnosis by standard definitions.

Results: Ten out of 94 patients with possible VP were excluded because no neuroimaging studies were available. The diagnosis at follow-up was

changed in 53 other patients. This included Parkinson's disease (PD) and various neurodegenerative disorders (21 patients), pseudobulbar palsy (9 patients), drug-induced parkinsonism (5 patients), isolated gait disorder (8 patients), and miscellaneous causes in 5 other patients. No definite diagnosis was possible in 5 patients with overlapping causes. Only 31 patients fulfilled the accepted criteria for VP. They comprised 1.57% of all parkinsonisms observed along the study period, and 3.94% out of 786 patients with a diagnosis of parkinsonism other than PD. For comparison, 40.4% of all secondary parkinsonisms were drug-induced.

Conclusions: Although some referral bias cannot be fully excluded, we conclude that VP is infrequent in specialized clinics.

P349

Development and validation of the MSA-QoL. A disease-specific health-related quality of life measure for multiple system atrophy

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Patient-based measures of health are important tools to assess the impact of chronic neurological disease on patients. Like other outcome measures they need to fulfill criteria for valid and psychometrically sound instruments. We here report the development and validation of a health-related quality of life measure for patients with multiple system atrophy (MSA), the MSA-QoL.

An initial scale was derived from interviews with 20 patients and carers, expert opinion, and review of the literature. Following a survey in 505 patients with MSA in the UK and the US, psychometric analysis including factor analysis was used to reduce the number of questions. The final questionnaire, which contained 40 questions in three subscales of motor, non-motor, and emotional/social functioning, was completed by 279 patients with MSA in the UK and the US. The questionnaire had a low number of missing data (6.8%), low floor (0%) and ceiling (2.0–4.6%) effects, good distribution scores, good internal consistency (Cronbach's alpha 0.83–0.93) and test-retest reliability (all $r > 0.9$). It was also shown to have good content, construct, and convergent validity as demonstrated by meaningful correlations with measures of disease severity and quality of life ($r = 0.5–0.8$, all $P < 0.001$), that compared favourably with the PDQ-39 and generic measures.

We conclude that the MSA-QoL is a patient-derived health-related quality of life measure for patients with MSA with good psychometric properties that reflects the difficulties patients with MSA are experiencing. It has superior content and convergent validity to the PDQ-39 in assessing Hr-QoL in patients with MSA. This instrument will provide patient-based and reliable data on the impact of MSA on patients Hr-QoL and should be incorporated in clinical trials in patients with this disorder.

P350

The PSP QoL (PSP-QoL): A validated, patient-based outcome measure for progressive supranuclear palsy

A.E. Schrag, C. Selai, A.J. Lees, N.P. Quinn, I. Litvan, A.E. Lang, et al. (UK; USA; Canada)

Validated, patient-based outcome measures are important tools to assess patients with chronic neurological disease. In progressive supranuclear palsy (PSP), no patient-based assessment measure exists, and no rating scale for this disorder has been validated to date. We report the development and validation of the first psychometrically developed patient-based scale for patients with PSP. An initial 87-item questionnaire was derived from in-depth interviews with 27 patients with PSP, expert opinion and review of the literature. This questionnaire was completed by 161 patient members of the PSP (Europe) Association in the UK, and an additional 64 patients with PSP recruited from movement disorders clinics in the UK and North America. The data were subjected to psychometric and clinimetric testing to create the final health-related quality of life instrument for patients with PSP (PSP-QoL). This scale contains 45 items in two subscales, the physical and the mental subscale. Analysis of results from a second survey in 158 patients with PSP revealed that the scale had few missing data (4%), scores in both subscales were evenly distributed, there

were no substantial floor and ceiling effects, and both subscales had excellent reliability (Cronbach's alpha 0.94 and 0.96). The PSP-QoL also had good internal validity with item-total correlations between 0.38 and 0.92 and an inter-scale correlation of 0.6, and factor analysis revealed little overlap between the subscales. Good convergent and divergent validity were demonstrated by meaningful correlations with measures of disease severity, disease duration, generic measures of health-related quality of life and measures of psychological well-being. The psychometric properties of the PSP-QoL were similar in the UK and North America, and in the clinic- and community-based samples. These results indicate that the PSP-QoL is a scientifically sound and clinically meaningful patient-based outcome measure for use in clinical trials in patients with PSP.

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MRI correlates of alien leg-like phenomenon in corticobasal degeneration

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Objective: To characterize radiographical correlates of alien leg-like phenomenon in corticobasal degeneration.

Background: The alien limb phenomenon is most commonly observed in patients with callosal disconnection. However, it has been observed in neurodegenerative diseases including Alzheimer's disease and most notably, corticobasal degeneration (CBD). Head magnetic resonance imaging (MRI) findings associated with CBD have never been correlated to specific clinical signs in CBD.

Methods: We present the clinical features and imaging studies of two patients with symptoms highly suggestive of CBD, including alien leg-like phenomena.

Results: Patient 1 presented with a 2-year history of progressive involuntary jerks and paresthesia in the right foot and subsequent bradykinesia, micrographia, and right hand jerks. The movements in her right leg were slow, spontaneous, complex, and semi-purposeful, and did not improve with levodopa. They intensified during voluntary movements and interfered with voluntary tasks. There was also ideomotor apraxia of the right foot, and mirror movements were seen in the right leg during intentional movements of the left leg. On MRI, there was focal atrophy and increased signal on fluid attenuation inversion recovery (FLAIR) images of the left parasagittal post-central and immediately adjacent left pre-central gyrus. Patient 2 presented with a 2 year history of progressive weakness, bradykinesia, and loss of motor control in the left foot. She reported the foot to "move on its own," and mirror movements were elicited in the left foot during intentional movements of the right foot. Similar findings of focal atrophy and increased signal on FLAIR images were seen in the right parasagittal frontoparietal region adjacent the right pre- and post-central gyri.

Conclusion: In patients presenting with suspected corticobasal degeneration and alien leg-like phenomenon, focal atrophy and increased signal on FLAIR images can be seen on MRI in the corresponding leg area of the homunculus and may represent the neurodegenerative changes responsible for their symptoms.

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Brainstem surface measurement by MRI is useful to differentiate Idiopathic Parkinson's disease (IPD), multiple system atrophy (MSA), and progressive supranuclear palsy (PSP)

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Objective: To evaluate the interest of brainstem surface measurement to differentiate IPD, MSA, and PSP on routine MRI.

Background: Severe atrophy involving the mesencephalon and the pons is well known from post mortem studies in respectively PSP and MSA, with relative sparing of both areas in IPD. In vivo, however, little is known about the discriminating power of MRI to differentiate these pathologies.

Methods: 335 patients (134 MSA, 123 PSP, 42% female, age 64.2 ± 8.2 , disease duration 4.2 ± 1.9), and 78 IPD (22%, $61.3 \pm 7.5 \pm 1.9$, $14.2 \pm$

5.3) suffering from clinically well-defined degenerative Parkinsonism underwent the same standardized MRI acquisition procedure including T1-weighted images in strict sagittal plane. On the medial slice, computerized surface measurement of both mesencephalon and pons was performed twice by the same radiologist blinded from clinical status. Reliability intra-observer was assessed with intra class coefficient (ICC) separately for IPD, and MSA and PSP together. Between group comparisons was performed using anova followed by t tests with the Bonferroni adjustment.

Results: Intra-observer reliability was excellent with $ICC > 0.9$ for both criteria in both populations. Mean surface of mesencephalon was not only significantly smaller in PSP group ($103 \pm 23 \text{ mm}^2$) versus both MSA ($138 \pm 22 \text{ mm}^2$) ($P < 0.0001$) and IPD ($153 \pm 22 \text{ mm}^2$) ($P < 0.0001$) groups, but also in MSA group versus IPD group ($P < 0.0001$). Mean surface of pons was also significantly smaller in both MSA ($184 \pm 53 \text{ mm}^2$) and PSP ($209 \pm 35 \text{ mm}^2$) groups versus IPD group ($228 \pm 31 \text{ mm}^2$) (with respectively $P < 0.0001$ and $P < 0.001$), and in MSA groups versus PSP ($P < 0.0001$).

Conclusions: Surface measurement of mesencephalon and pons on the medial sagittal plane of T1-weighted MRI is useful to routinely differentiate PSP, MSA, and IPD.

P353

Dopamine transporter imaging in the differential diagnosis between vascular parkinsonism and idiopathic Parkinson's disease

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Objective and Background: [^{123}I]-FP- β -CIT SPECT is a sensitive marker of nigrostriatal dopaminergic degeneration. We investigated whether [^{123}I]-FP- β -CIT SPECT imaging distinguishes patients with clinically suspected vascular parkinsonism (VP) from patients with idiopathic Parkinson's disease (IPD).

Methods: Thirty-three patients who fulfilled rigid clinical criteria for VP (mean \pm SD: age, 70.2 ± 4.5 years; disease duration, 4.5 ± 6.3 years), 100 IPD patients (age, 67.9 ± 7.6 years; disease duration, 5.3 ± 7.9 years), and 20 healthy persons (age, 60.9 ± 6.2 years) underwent [^{123}I]-FP- β -CIT SPECT imaging.

Results: Age-corrected striatal [^{123}I]-FP- β -CIT binding was reduced on average by 46% in IPD but was near normal in the VP group ($P < 0.001$). The left-right asymmetry of striatal [^{123}I]-FP- β -CIT binding was significantly increased in the IPD group compared with normal controls and the VP group ($P < 0.025$). Moreover, caudate-putamen ratios were significantly increased in IPD compared with both VP patients and healthy controls ($P < 0.001$).

Conclusions: Our findings suggest that the presynaptic dopaminergic deficits seen in IPD are absent in VP. [^{123}I]-FP- β -CIT SPECT imaging may be useful to help distinguish between IPD and VP patients.

P354

The relationship between histopathological features of progressive supranuclear palsy and disease duration

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Objective: To review semiquantitative data collected as part of the diagnostic evaluation of cases submitted to the Society of Progressive Supranuclear Palsy Brain Bank for any relationships that might exist between disease duration and lesion burden.

Background: Pathological findings in progressive supranuclear palsy (PSP) include neuronal loss and gliosis in selective subcortical regions associated with tau-positive intracellular lesions, including neurofibrillary tangles (NFT), threads, oligodendroglial coiled bodies (CB), and tufted astrocytes (TA). In PSP, ultrastructural studies have shown that many of the threads are cell processes from oligodendrocytes. No data exist regarding the relationship of disease duration to lesion burden.

Methods: Retrospective review of the clinical, neuropathologic, and genetic data on PSP cases that lack any other major pathologic process. At the time of neuropathological assessment, an assessment of the severity of NFT, threads, CB, and TA is made for each case of PSP on tissue sections immunostained for phospho-tau using a 4-point scale (0 = none, 1 = mild, 2 = moderate, and 3 = severe) in 18 brain regions. Statistical analysis was used to explore possible relationships between lesion burden and disease duration. Apolipoprotein E (*APOE*) and tau (*MAPT*) genetic variants was also assessed.

Results: We identified 97 cases of pure PSP with adequate medical records to assess disease duration. 58% were male, mean disease duration was 6.7 years, *MAPT* H1 haplotype frequency was 93%, and 15% were carriers of *APOE* e4. There was a strong negative association between disease duration and CB ($P < 0.001$), and between disease duration and threads ($P < 0.001$) independent of region of interest. A similar negative association was found for total tau burden. There were no associations between disease duration and Braak stage, age at death, gender, *MAPT* H1 haplotype, or *APOE* e4.

Conclusion: This data suggests that in PSP, as the disease duration increases there is a surprising decrease in the density of oligodendroglial CB and threads and an overall reduction in tau burden, independent of age, gender, *APOE*, and *MAPT* H1 genetic variants. Neuronal tau-positive lesions in PSP are pre-tangles and NFT that undergo resorption when the neuron dies. It remains unknown if a similar process affects glial cells in PSP.

P355

Motor progression of multiple system atrophy (MSA): A prospective study using the unified MSA rating scale (UMSARS)

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Background: MSA is a sporadic neurodegenerative disorder characterised by the gradual onset and relentless worsening of symptoms. Prospective natural history studies using disease specific scales are lacking.

Objective: We assessed rates of progression of disability including motor function as well as activities of daily living (ADL) and mental function. The following scales or questionnaires were applied on regular therapy at two time points: UMSARS II (for motor function); UMSARS I, SE ADL and UPDRS II (for ADL); UPDRS I, Beck Depression Inventory (BDI), MMSE (for neuropsychiatric features); HY Parkinson's Staging, UMSARS IV, and a 3-point severity scale (SS3) (for global disability).

Results: 76 patients (possible MSA 14.5%, probable MSA 85.5%; MSA-P 61.8%, MSA-C 38.2%) were assessed twice with a mean delay of 6.4 months. UMSARS II scores progressed by 11.8% ($P < 0.0001$) and UMSARS I by 8.8% ($P < 0.0001$) in relation to the respective maximum scores. The different UMSARS II subscores showed differences in their rates of decline ranging from 7.8% for tremor ($P < 0.0001$) to 13.9% for akinesia ($P < 0.0001$). 67% of the variation of UMSARS II change was solely due to the change in akinesia ($P < 0.0001$), 94% were explained by akinesia, PIGD, cerebellar dysfunction and tremor ($P < 0.0001$). MSA-P deteriorated more than twice in UMSARS I scores than MSA-C patients ($P = 0.005$), whereas UMSARS II showed no difference. There was no significant progression of mental function. We found low but significant inverse correlations between (1) the change in UMSARS II scores and (2) baseline scores of SS3 ($r = -0.253$, $P = 0.036$), HY staging ($r = -0.32$, $P = 0.007$), UMSARS II subscore akinesia ($r = -0.267$, $P = 0.026$), and UMSARS II subscore cerebellar dysfunction ($r = -0.273$, $P = 0.023$).

Conclusion: This is the first study showing a rapid deterioration of the motor disorder, in particular akinesia, and, to a lesser degree, of ADL in MSA using the disease specific UMSARS. Motor progression was associated with low motor or global disability as well as low akinesia or cerebellar subscores at baseline. These data facilitate the planning and implementation of future neuroprotective intervention trials.

P356

Staging disease severity in movement disorder tauopathies: Brain atrophy separates progressive supranuclear palsy from corticobasal degeneration

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Objective: To investigate the applicability of a recently developed staging scheme for frontotemporal dementia (FTD) [1] to the progression of brain atrophy in progressive supranuclear palsy (PSP) and corticobasal degeneration (CBD).

Background: The movement disorders PSP and CBD both deposit tau in degenerating neurons and are considered to be tauopathies, along with FTD. Despite different clinical phenotypes in FTD, disease progression is reflected by a systematic degree and distribution of brain atrophy which can be graded by applying a simple staging scheme.¹ This includes both cortical and subcortical degeneration and relates directly to the degree of neuronal loss as well as the severity and duration of clinical features.¹ While the timing of clinical events, particularly in PSP, is well documented, the progression of brain changes in the movement disorder tauopathies is less well understood.

Methods: The recently developed scheme for staging tissue degeneration in FTD¹ was applied to pathologically confirmed PSP (n = 24) and CBD (n = 9) cases and correlated with clinical indices.

Results: In contrast to FTD, the majority of PSP cases had limited or no visible atrophy, while the pattern of atrophy in CBD cases conformed to the existing staging scheme (all but one case exhibiting substantial visible tissue atrophy). Atrophy in CBD first occurred in the mediosuperior frontal cortex, the orbitofrontal cortex, and the hippocampus, then progressed to the basal ganglia and other frontal cortices before affecting the white matter and the rest of the temporal lobe. Despite similar clinical severity and disease duration between groups, there was a marked difference between the PSP and CBD cases in pathological disease stage ($\chi^2 = 8.86$, $P = 0.03$). The difference in cytotoxicity was not due to differences the presence or severity of clinical symptoms or disease duration, as these were not statistically different between groups.

Conclusions: PSP appears to be less cytotoxic than other tauopathies, while CBD appears similar to other pathological forms of FTD.

Reference

1. Broe M, et al. *Neurology* 2003;60:1005–1011.

P357

Progressive parkinsonism in a welder due to manganese intoxication
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Background: Chronic exposure to manganese (Mn) dust as in case of welding may cause neurological symptoms mostly referable to the extra-pyramidal system. In most of the cases, the clinical picture is compatible with parkinsonism resistant to treatment. We present a welder with akinetic-rigid parkinsonism.

Case: A 31-year-old man with an occupational history of welding for 10 years since the age of 19, was admitted due to progressive inbalance, gait problems, frequent falls, and bradykinesia for 1.5 year. His neurological examination revealed akinetic-rigid parkinsonism accompanied by severe postural instability, dystonia, typical cock gait, action dystonia, and pyramidal findings. His MRI of the brain showed bilateral symmetric T1-weighted hyperintense patterns in the region of the basal ganglia, being most prominent in the globus pallidum. He was unresponsive to dopaminergic therapy.

Conclusion: In the present case, the median latency period between manganese exposure and development of parkinsonism was 10 years. The clinical course showed a rapid progression with lack of response to levodopa and associated with distinctive T1-weighted hyperintense patterns in the globus pallidum on the MRI. The diagnosis of manganism requires a history of manganese exposure in combination with physical and radiological findings. Welders often use a visor to protect the eyes but ignore to use tools to avoid inhalation of the fume. Since chronic Mn toxicity may

cause late-onset irreversible neurologic disturbances and serious disability, welders should be informed about this hazard.

P358

Health-related quality of life (HR-QoL) in multiple system atrophy (MSA)

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Objective: To assess the nature of health-related Hr-QoL in MSA.

Background: Although MSA is a chronic progressive disorder with considerable and progressive disability, little is known about patients' own evaluation of the impact of this disorder on their lives.

Methods: The following scales or questionnaires were applied: The generic Medical Outcome Study Short Form health survey (SF-36), Euro-QoL 5D (EQ-5D) (for Hr-QoL); UMSARS II (for motor function); UMSARS I, SE ADL and UPDRS II (for ADL); Composite Autonomic Symptom Scale (COMPASS) (for dysautonomia); UPDRS I, Beck Depression Inventory (BDI), MMSE (for neuropsychiatric features); HY Parkinson's Staging, UMSARS IV, and a 3-point severity scale (SS3) (for global disability).

Results: We analyzed 115 MSA patients (MSA-P: 62.6%, MSA-C: 37.4%; possible MSA: 22.6%, probable MSA: 77.4%). Depression (BDI cut off: 16 points) was common (46.3%). Hr-QoL scores compared to normative age-matched values and PD after similar disease duration showed lower values in MSA ($P < 0.001$). MSA-P patients had worse Hr-QoL scores than MSA-C patients, in particular for pain ($P < 0.05$). Patients with possible MSA showed better SF-36 subscores on physical items and pain than those with probable MSA ($P < 0.05$). There was a significant inverse correlation between (1) Hr-QoL and (2) UMSARS II, in particular the UMSARS II subscore postural instability and gait disorder, measures of global disease severity, the BDI, and the COMPASS. The COMPASS score and UMSARS II speech subscore predicted 47% of the variance of SF-36 physical scores ($P < 0.05$) and the BDI and COMPASS score predicted 54% of the variance of the SF 36-mental summary score ($P < 0.05$).

Conclusions: MSA is associated with a significant impairment of Hr-QoL. Motor impairment, autonomic dysfunction and depressive symptoms appear to be the main predictors for poor quality of life and should therefore be recognized as major therapeutic targets in the management of MSA.

P359

Basal ganglia cryptococcal abscesses presenting with parkinsonism in a non-immunocompromised patient

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Objective: To describe a case of parkinsonism associated with cryptococcal abscesses in basal ganglia in a patient without immunodeficiency.

Background: Parkinsonism related to infectious has been described in AIDS patients as part of HIV encephalopathy or opportunistic infections. Two AIDS patients with cryptococcal infection presenting with parkinsonism have been reported.^{1,2} There is another report of parkinsonism associated with neurocryptococcosis in a immunocompromised patient with chronic lymphocytic leukemia.³

Case report: A 42-year-old female was admitted to the hospital with progressive severe headache of onset 3 weeks before. There was a history of mild arterial hypertension, dyslipidemia, and weight loss in the previous months. First neurological examination was normal. She was submitted to extensive laboratory workup, including serological studies for HIV, cytomegalovirus, Epstein-Barr virus, viral hepatitis, toxoplasmosis, brucellosis, and syphilis. All results were negative. MRI showed only enlarged Virchow-Robin spaces. CSF analysis demonstrated 106 leukocytes/mm³ (75% of neutrophils), protein 52 mg/dL, and glucose 56 mg/dL. The India ink preparation of centrifuged CSF revealed budding yeast cells and surrounding capsule. CSF culture confirmed *Cryptococcus neoformans*. A small pulmonary nodule was demonstrated on thorax CT scan. She was started on

amphotericin B (0.5 mg/kg/day). Despite treatment, the patient evolved with rigidity, bradykinesia, resting tremor on the right arm, postural instability, dysarthria, trunk and limb ataxia. A new MRI showed greater enlargement of Virchow-Robin spaces and lesions suggestive of cryptococcal abscesses on basal ganglia. Flucytosine (100 mg/kg/day) was added to amphotericin B. After completion of treatment, tremor at rest and ataxia disappeared, and bradykinesia, rigidity, and postural instability improved significantly. There was resolution of abscesses on MRI.

Conclusion: To our knowledge, this is the first case-report of parkinsonism associated with neurocryptococcosis in an immunocompetent patient. The acute development of parkinsonism should alert to the possibility of infectious etiologies.

References

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2. Bouffard et al. *Mov Disord* 2003;18:1354–1357.
3. Wszolek et al. *Mov Disord* 1988;3:271–273.

P360

Atypical Wilson disease presenting hemiparesis as an initial manifestation

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Objective: To report a case of Wilson disease presenting hemiparesis as an initial symptom and following parkinsonism responsive to D-penicillamine medication.

Background: Wilson disease (WD) is a hereditary disorder of copper metabolism manifesting hepatic cirrhosis and basal ganglia damage. Most of the patients with WD may display variable neurological symptoms such as hand tremor and clumsy, personality change, speech disturbance, dysphagia, drooling, and gait disturbance, which are well established as initial symptoms in adult WD. Hemiparesis as an initial symptom as a result of unexplained young-age stroke has not been reported in WD.

Case: A 37-year-old woman suffered from abrupt onset of right hemiparesis 2 months ago and was diagnosed as left internal capsular infarct. Although right hemiparesis was slowly improved, she complained of gradually aggravating left-side weakness, resting tremor on hands, rigidity, and gait disturbance. There was no family history and past medical history. We could not detect any risk factors for young-age stroke by history or laboratory tests for hematological disease, heart disease, vasculitis, or inherited metabolic disease. Laboratory studies including liver function test, serum ceruloplasmin, serum copper, and urine copper were abnormal and ultrasonography presented liver cirrhosis. Analysis of the WD gene showed that she was carrying the M7691 mutation, which was well known but not popular. Finally she was diagnosed as WD. Her symptoms were improved by D-penicillamine and pyridoxine medication.

Conclusion: For now, we describe a case of WD presenting hemiparesis as an initial symptom. Although hemiparesis resulted from lacunar infarction, we could not detect any etiology of young-age stroke except WD. It is not clear whether young-age stroke can be ascribed to pathological changes in WD. We assume that the study on the correlation between WD and young-age stroke will be necessary.

P361

Subclinical REM sleep behavior disorder (RBD) in two patients with corticobasal degeneration (CBD)

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Objective: To report two patients with CBD and RBD.

Background: The diagnostic features of RBD include harmful sleep behaviors and dream enactment with loss of skeletal muscle atonia during REM sleep. The polysomnographic (PSG) finding of REM sleep without atonia has been described as *subclinical* RBD. CBD is a rare progressive neurodegenerative disease. To date, only three cases of RBD in CBD have been reported in the literature. We present two patients who showed *subclinical* RBD that fulfilled clinical diagnosis criteria for CBD.

Case 1: A 60-year-old female progressively developed since 1995 a Balint's-like syndrome, clumsiness, bradykinesia, and apraxia in her right

arm. Over the past 2 years profound cognitive decline has been evident with aphasia and ideational and motor apraxia. The extrapyramidal abnormalities have generalized, and focal myoclonus has been detected in the right arm. Brain MRI disclosed asymmetric atrophy predominantly in the left frontal cortex. PSG studies showed tonic chin EMG activity during REM sleep.

Case 2: A 75-year-old man was admitted for postural instability. Since 2001 he has progressively developed hypomimia and clumsiness in his right hemibody. His neurological examination showed bradykinesia, dystonic posture in his right arm, neglect, and levitation. He also presented motor and dressing apraxia and sporadic myoclonus. Cognitive evaluation disclosed a dysexecutive and visuoconstructive deficit. Brain MRI presented left frontal temporal and parietal atrophy. PSGs revealed loss of skeletal muscle atonia during REM sleep.

Discussion: Our patients presented increased tonic EMG activity during REM sleep in the setting of a CBD. The relationship between RBD and REM without atonia remains unknown; nonetheless, this latter has been recognized as a *subclinical* RBD. CBD principally involves cortical and subcortical structures. Recent studies suggest an additional compromise of neurons in the nuclei of the brainstem and the pedunculopontine pathways. Interestingly, these regions have been implicated in the generation of atonia during REM sleep. In agreement with previous reports, these findings support a widespread impairment in CBD. REM sleep abnormalities merit further investigation in CBD to better identify the precise neuronal structures involved in this taupathy.

P362

LRRK2/PARK8 in families with parkinsonism

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Objective: To report a discovery of mutations in *LRRK2* gene on chromosome 12p11.2-q31.1 in parkinsonian families.

Background: We have longitudinally followed two large multigenerational parkinsonian kindreds: Family D (Western Nebraska) since 1992 and Family A (German-Canadian) since 1991. Family D phenotype is indistinguishable from typical sporadic Parkinson's disease (PD). During the study period 4 autopsies were performed. Neuronal loss and gliosis were present in substantia nigra (SN) in all 4 cases and in one case this was the only abnormality without any distinctive histopathologic findings, in two others Lewy bodies (LB) were seen (in brain stem only in one case and in widespread distribution in another) and in the fourth case (with SGP) tau depositions were identified. Family A phenotype is more complex and includes levodopa responsive parkinsonism occurring alone or in combination with dementia, dystonia, and amyotrophy. During the study period 2 autopsies were performed and some material was retrieved from the third one performed in 1975. Neuronal loss and gliosis were present in SN in all cases. No LB were seen but the abundant ubiquitin and eosinophilic granules were identified together with mild loss of anterior horn cells, senile plaques, and some neurofibrillary tangles. Last year we linked both kindreds to PARK8 locus on chromosome 12q12.

Methods: High-resolution recombination mapping and candidate gene sequencing were performed in Families D and A.

Results: We discovered mutations in a gene encoding a large, multifunctional protein, *LRRK2* (leucine-rich repeat kinase 2) in Family D (R1441C) and Family A (Y1699C). Sequencing 44 additional parkinsonian families demonstrated the presence of 3 other missense mutations and 1 putative splice site mutation in smaller kindreds from the USA and Germany. The novel gene encodes a large, multifunctional ROCO protein that includes a protein kinase of the MAPKKK class.

Conclusions: The identification of *LRRK2* may have a significant implication for the further understanding of pathophysiological mechanisms of neurodegeneration.

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The effects of rapid repetitive transcranial magnetic stimulation over the posterior fossa on gait in patients with multiple system atrophy

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Objective: To evaluate the effects of rapid-TMS over the posterior fossa on gait in patients with MSA.

Background: Powerful low-frequency transcranial magnetic stimulation (TMS) (2.5 time the motor threshold; 0.16 Hz) over the cerebellum was found to improve posture and gait in patients with spino-cerebellar degenerations.¹ However, this method of TMS is potentially dangerous because of seizures and vigorous painful contractions of cervical muscles. We tested the hypothesis that high-frequency TMS of markedly lesser power delivered over the posterior fossa could also improve locomotion in patients with multiple system atrophy (MSA).

Methods: Three weeks course of r-TMS (20 treatment sessions, 10 Hz, 90% of motor threshold) was given over the occipital external protuberantia in 11 patients with MSA (7 MSA-P; 4 MSA-C). Extrapyramidal and cerebellar signs were evaluated according to Unified Parkinson's Disease Rating Scale (UPDRS) and International Cooperative Ataxia rating scale (ICARS). The motor item's total scores were calculated by summing of scores within the one UPDRS or ICARS item. Posture and gait parameters were assessed according to "10-10," "Timed Up and Go" exams, and averaged stride time. Examinations were done before and after TMS course, and every month post-TMS to reveal carry-over effect. Mean values and standard deviation (SD) were compared using paired *t*-test.

Results: Significant decrease of total UPDRS and ICARS scores ($P < 0.001$ and $P < 0.05$, respectively) were observed in patients with MSA-P. This improvement was observed in gait difficulties ($P < 0.001$), enhancement of walking capacities ($P < 0.03$), shortening of fast gait time ($P = 0.055$, trend) and average stride time ($P < 0.018$). In 3 MSA-P patients the improvement in gait extended up to 3 month post-TMS. Other motor items did not change in both subtypes of MSA. No locomotion improvements were obtained in patients with MSA-C. No adverse effects were reported.

Conclusions: Rapid TMS over a period of 3 weeks was an effective and safe therapeutic intervention to improve gait in patients with MSA-P. Controlled study concerning the TMS influence on posterior fossa structures is warranted.

Reference

1. Shiga et al., 2001.

P364

Restless legs in idiopathic Parkinson's disease

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Objective: To evaluate the frequency of Restless Legs (RLS) in Idiopathic Parkinson's disease (IPD) patients and its relation to PD duration, HY stage, and motor fluctuations.

Background: Lower limb motor restlessness is frequently reported on by IPD patients. Levodopa responsiveness is a feature of both IPD and RLS, raising the issue of a shared pathophysiology between the two disorders. Data on RLS frequency in IPD are conflicting, with some studies reporting increased RLS prevalences in IPD, while others failed to detect differences in RLS frequency between IPD cohorts and the general population.

Methods: We conducted a prospective survey of RLS in IPD patients using IRLSSG questionnaire.

Medical records were reviewed for age, PD duration and motor fluctuations (wearing-off, on-off fluctuations). Data was compared between IPD patients with and without clinically defined RLS.

Results: Out of 113 IPD patients, 28 (24%) met all IRLSSG essential criteria and were classified as PD/RLS (+). The remaining 85 patients constituted the PD/RLS (-) group.

PD/RLS (+) were younger than PD/RLS (-) patients (62 vs. 69 years, $P < 0.004$) and had similar PD durations (8.8 vs. 9.5 years, $P = 0.57$).

RLS preceded PD by an average of 8.5 years in 5 cases, while RLS onset occurred after the manifestation of PD in the others (mean latency 4.5 years).

PD/RLS (+) had lower HY scores in "on" and a tendency to lower UPDRS III scores (II vs. III, $P = 0.02$ and 25 vs. 31 $P = 0.06$).

Motor fluctuations occurred with similar frequencies in both groups (60% vs. 61%, $P = 0.94$).

61% of PD/RLS(+) patients reported on an urgency to move legs or unpleasant sensations related to wearing off periods. In contrast, only 17% of PD/RLS (-) patients reported such symptoms related to wearing-off periods ($P < 0.001$).

Conclusions: RLS symptoms were present in 24% of this IPD population. This appears a twofold increase on reported RLS prevalences in the community. 61% of PD/RLS (+) patients reported on urgency to move legs or unpleasant sensations related to wearing-off periods, raising the possibility of RLS phenocopies in fluctuating IPD patients. Only a minority of IPD patients (17%) had unequivocal clinical evidence of RLS phenomenology before the onset of IPD. Studies on the risk of IPD in RLS patients are warranted.

P365

Intra-rater reliability of the unified multiple system atrophy rating scale (UMSARS)

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Objective and Background: We have recently reported on the validity and inter-rater reliability of the motor part of the Unified Multiple System Atrophy Rating Scale (UMSARS-II). The aim of the following study was to assess the intra-rater reliability of the UMSARS-II.

Patients and methods: Forty patients with MSA in four centres were rated twice by four raters per centre (two senior and two junior raters) comparing the initial life rating and a subsequent video rating separated by over 3 months. Weighted kappa statistics were calculated for the individual UMSARS-II items, the intraclass correlation coefficient (ICC) for the motor UMSARS score.

Results: The intra-rater reliability for the following UMSARS II items was excellent [$k(w) > 0.8$]: Heel-Shine-test, posture, gait, body sway, and arising from chair; the intra-rater reliability for the following UMSARS II items was substantial [$k(w) = 0.5-0.8$]: rapid alternating movements of hands, leg agility, finger taps, facial expression, tremor at rest, action tremor and speech. Intra-rater reliability of oculomotor dysfunction (item) was only moderate. Generally, intra-rater agreement for the UMSARS-II items was comparable between senior and junior raters. Only item 9 (leg agility) showed a k-value discrepancy of >0.4 among senior and junior raters. The ICCs for the total motor UMSARS score were 0.98 for the senior raters and 0.97 for the junior raters.

Conclusion: Based on our findings, the UMSARS-II was found to have satisfactory intra-rater reliability in this sample. Thus, the UMSARS II appears to be a multidimensional, reliable and valid scale for semi-quantitative clinical assessments of MSA patients.

P366

Atypical familial PSP

M.H. Anca, M. Loberboim, D. Lev (Israel)

Objective: To report a familial case of probable PSP, with similar phenotype and paradoxical correlation between clinical and striatal hypodopaminergic state.

Background: Progressive Supranuclear Palsy (PSP) is a form of Parkinsonism associated with the *tau* gene. Rare familial forms of PSP have been described. Recent publications pointed out the absence of *tau* mutation and the underestimation of familial PSP because the wide phenotypic expression. The brain atrophy on MRI is associated with degeneration of dopaminergic terminals in striatum on PET/SPECT.

Design: Two siblings of non-consanguineous parents are described: C.D., a female aged 30 and C.G., a male aged 33, both in good general

health. C.D. started in childhood with tics and compulsive laugh. At age of 25 a hand tremor and learning difficulty appeared with slowness, unsteady walk, and falls. Pyramidal signs associated with axial rigidity, low postural reflexes, vertical gaze palsy, and dysarthria were found. Psycho-cognitive and physical therapy preserved her motor skills; she remained stable for 2 years and continued studying. Extensive metabolic and molecular diagnostic workup was normal. Brain MRI revealed general brain atrophy. DAT scan showed absent binding in both putamen and mild reduction in both caudate nuclei. C.G. developed normally with some irritable behavior. At age of 27 a hand tremor was noted. After a minor accident his behavior became aggressive and his gait spastic. The clinical signs, stable for 3 years are: leg spasticity, mild rigidity but preserved postural reflexes, staring gaze with mild vertical limitation, facial twitches, and compulsive speech. The diagnostic workup was normal as was his sister's. The brain MRI showed brain atrophy. DAT scan showed no DAT binding in both putamen and severely reduced in both caudate nuclei.

Conclusion: Despite the young age of disease onset and slow progression, according to clinical and imaging findings the probable diagnosis in these 2 siblings is atypical familial PSP. There are no previous reports on such a correlation between clinical severity and imaging findings. The paradoxical association between milder form of the disease and more severe dopaminergic depletion raises the question whether the role of dopaminergic system is primary in the disease generation or successive to other lesions. Further detailed studies are needed to answer to this dilemma.

P367

Association of dementia with parkinsonian signs in the elderly general population in central Spain

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Objective: To determine the association of parkinsonism and dementia in a census-based sample of elderly population.

Background: The association of parkinsonian signs with dementia in the general elderly population is unclear.

Methods: In a census-based sample in Leganes, a town of Central Spain considered representative of the Spanish population, 517 subjects over 70 years of age were evaluated. We asked whether they had a prior diagnosis of Parkinson's disease (pPD), and whether they used neuroleptic drugs. Following a neurological exam and motor subscale of UPDRS, parkinsonism was defined as score >1 in UPDRS in 2 or more of tremor, rigidity, akinesia, and postural reflex alteration. Dementia diagnosis was made by DSM-IV criteria.

Results: pPD diagnosis was present in 21 cases. The remaining subjects were classified as: 1) no parkinsonism, UPDRS = 0 in 286 cases; 2) no parkinsonism, UPDRS > 0 in 153 cases; 3) parkinsonism in 57 cases, of which 6 were attributed to neuroleptic drugs. Dementia was present in 33.3% of pPD cases. The following percentage of cases received a diagnosis of dementia: 1) no parkinsonism, UPDRS = 0: 3.4%; 2) no parkinsonism, UPDRS > 0: 17.6%; and 3) parkinsonism: 40.3%. ($\chi^2 = 70.19$, $P < 0.0001$).

Conclusions: Parkinsonian signs are common in the general elderly population. The prevalence of dementia increases as any parkinsonian signs appear, and even more when frank parkinsonism is present.

P368

Elevated titers of anti-thyroid antibodies in patients with multiple system atrophy, unexpected observation

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Objective: To investigate the prevalence of elevated anti-thyroid antibodies (anti-TPO Ab) and anti-thyroglobulin antibodies (anti-TG Ab) in patients with multiple system atrophy (MSA).

Background: MSA is a neurodegenerative disorder characterized by progressive loss of neuronal and oligodendroglial cells in numerous sites in the central nervous system. The etiology of the cell loss is still unknown. Autoimmune mechanisms have also been suggested as potential causes of MSA.

Methods: Serum levels of anti TPO Ab and anti-TG Ab were tested in 13 consecutive euthyroid patients over 40 years of age that fulfilled the clinical diagnostic criteria for probable MSA.

Results: 13 MSA patients (age 56.46 ± 16.5 year, 5 males) took part in the study. 7 patients had parkinsonian type of MSA (MSA-P) and 6-cerebellar type (MSA-C). In all patients thyroid stimulating hormone (TSH) and free thyroxin (FT4) were normal. Anti-TPO Ab were above normal (average level of 315.25 ± 241.4 IU/mL) in 4 patients (30.8%)—two men and two women. Three patients with elevated Anti-TPO Ab had MSA-C (50% of MSA-C patients □ 23% of all investigated MSA patients) and 1-MSA-P (14.3% of MSA-P patients; 8% of all investigated patients).

Anti-TG Ab were above normal in 2 other MSA-P patients (man and woman) with levels of 135 IU/ml and 185 IU/ml, respectively (normal value <100 IU/mL).

Conclusion: The prevalence of elevated levels of anti-TPO Ab and anti-TG Ab were significantly higher in patients with MSA when compared to published data for euthyroid control population of the same age group. Elevated anti-thyroid antibodies titer in MSA patients may suggest of an autoimmune contribution to the pathogenesis of MSA. Larger controlled studies are needed to support our preliminary observations that may have clinical implication.

P369

Frequency and nature of dystonia in MSA and PSP

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Objective: Published data on the frequency of dystonia in MSA and PSP is equivocal (MSA: 12–40%; PSP 8–46%), and so is data on its distribution and its time of onset. We reviewed the clinical characteristics of dystonia in patients participating at 3 German sites of the multicentric NNIPPS-trial.

Methods: 81 Patients with PSP [n = 39; 15 female; mean age at onset 63.6 years (54–77)] or MSA [n = 42, 23 female; mean age of onset 57.9 years (45–72)] were prospectively seen every 3 months for 3 years using a standardised examination focusing on dystonia. The frequency of dystonia, its patterns of distribution and natural course was analysed.

Results: 68% of patients with MSA and 77% of those with PSP developed dystonia at some point of the disease. In MSA, most common was dystonia of the trunk (31%) and lower limbs (29%). Anterocollis was found in 26%; dystonia was observed in the face in 24% and in the upper limbs in 21%. At inclusion, 79% of MSA patients with dystonia already had dystonic signs, which chiefly occurred axially (54%). In those patients in whom dystonia developed after inclusion, the first manifestation was Pisa-Syndrome in 4 patients, and anterocollis and limb dystonia in 1 patient, each.

In PSP, dystonia was more common and occurred in all parts of the body equally: retrocollis or cervical dystonia was observed in 56%; in 49% dystonia was truncal (either in extension or Pisa-Syndrome), in 49% facial, in 51% in upper limbs, and in 44% in lower limbs. 50% of PSP patients with dystonia already had dystonic signs at inclusion, which were axial in 66%. In those patients in whom dystonia occurred after inclusion, the first manifestation was in the upper limbs in 4 patients, in the lower limbs, face, or neck in 2 patients each and in the trunk in 1 patient. In 4 patients the onset was multifocal.

At the time of the first manifestation of dystonia, PSP patients with dystonia had a greater UPDRS III score than those without. In MSA, there was no difference.

Conclusion: Dystonia in MSA and especially in PSP is more common than previously reported and can be observed quite early in the course of the disease. In PSP as well as in MSA axial muscles are prone to dystonia and far more common—though less specific—than the so-called “red flags” retrocollis and anterocollis obviously is truncal dystonia.

P370

Diagnostic value of ^{123}I -Ioflupane SPECT in psychogenic parkinsonism

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Objectives: To evaluate ^{123}I -Ioflupane SPECT in the diagnosis of suspected psychogenic parkinsonism (PsyP).

Background: PsyP can be clinically difficult to differentiate from Parkinson's disease (PD). Striatal dopamine transporter (DAT) imaging provides information about nigrostriatal integrity and can separate PD from parkinsonism without nigrostriatal degeneration. Nigrostriatal pathway is presumed to be normal in PsyP. We performed ^{123}I -Ioflupane SPECT in five patients with suspected PsyP.

Clinical Cases: Five patients (four women and one man, mean age 56 years old) with a diagnosis of PD under dopaminergic treatments, were referred to our Movement Disorder Unit. Disease duration ranged from 2 to 12 years and Hoehn-Yahr stage from II to V. All five patients presented rest tremor, bradykinesia, and increased muscular tone, but the presence of atypical features raised the suspicion of PsyP. Disease's onset was acute in two patients and in one of them appear after foot surgery. The clinical course was non-progressive in three cases. Rest tremor, sometimes with action component, fluctuated in intensity during examination and decreased with distraction or concentration. Increased paratonic muscular tone without cogwheeling were present. All patients referred vague and bizarre somatic symptoms and depression and anxiety were present in four. Therapy with adequate doses of levodopa or dopaminergic agonists did not significantly benefit any patient.

Results: ^{123}I -Ioflupane SPECT disclosed normal striatal tracer uptake in all five patients.

Conclusion: Five patients with suspected PsyP had normal DAT imaging studies. Although such studies can be normal in a small percentage of neurodegenerative parkinsonism, a normal ^{123}I -Ioflupane SPECT indicates an absence of an underlying nigrostriatal degeneration and can support the diagnosis of PsyP.

P371

Motor fluctuations in juvenile parkinsonism—Management dilemma

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Objective: We present two cases of Juvenile parkinsonism to highlight the management problems in such young patients.

Background: Juvenile parkinsonism is being increasingly recognized in the

Indian subcontinent, often post encephalitic. Such patients are often responsive to levodopa (L dopa) but like young onset Parkinson's disease (PD) tend to have very early motor fluctuations.

Case 1: An 8-year-old boy, born of a 3rd degree consanguineous marriage presented with a progressive generalized dystonia with marked akinesia. He was bedridden and mute. He had dramatic improvement with dopamine supplementation and started walking without assistance within 1 month with marked improvement of speech. Within a year he presented with peak dose dyskinesias and wearing off phenomenon. He required 400 mg of L Dopa + Carbidopa (24 kg). During the off periods he was markedly akinetic and dystonic. After adjustment of the L Dopa doses he is barely functional.

Case 2: An 8-year-old boy with an encephalitic illness at the age of 5 years presented with an akinetic rigid syndrome of 2 years duration. He was bedridden and mute. His MRI Brain (Figure 1) showed a T₂ hyperintense lesion in the midbrain involving substantia nigra. After an initial period on Bromocriptine he was started on L Dopa. Within 2 years he presented with wearing off phenomenon and peak dose dyskinesias. At present (13 years of age) he requires 9 mg of Ropinirole and he is on 400 mg of L Dopa + Carbidopa to remain on with dyskinesias.

Conclusion: Management of juvenile parkinsonism is extremely challenging and difficult. Post-encephalitic parkinsonism may be progressive, and as difficult to treat as juvenile PD. The issues involved in DBS at this early age need to be studied [Figure 1].



Figure 1. Abstract 371

P372

Can the clonidine-growth hormone (GH) stimulation test (CGHST) distinguish multiple system atrophy and Parkinson's disease early in the course of illness?

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Introduction: The Clonidine-growth hormone stimulation test (CGHST) differentiates patients with a confirmed diagnosis of Multiple System Atrophy-Parkinsonian type (MSA-P) from Parkinson's disease (PD). Its role to distinguish the two parkinsonian disorders early in the course of illness has not been examined.

Objective: Ability of clonidine growth hormone stimulation test to differentiate MSA-P from PD within 3 years of onset of motor symptoms.

Participants: Parkinsonian patients aged 16–75 years were classified into PD (n = 112) using UKPDSBBR criteria and MSA-P (n = 12) using Gilman's criteria and prospectively recruited. None had medical conditions causing autonomic dysfunction, or cerebellar signs.

Methods: CGHST: Participants were tested in a practical "off" state after overnight fasting. Blood samples were collected at baseline and four serial samples were collected at intervals of 15 min after iv Clonidine (2 mg/kg). Samples were analyzed for Human GH levels using radioimmunoassay kits from National Institute of Health, Bethesda, USA, with reference preparations from National Hormone Pituitary Program, Torrance, USA.

Results: PD and MSA-P had a similar age at presentation (55 ± 11 and 59 ± 6.2 , $P = 0.13$) and duration of motor symptoms (1.7 ± 0.7 and 1.8 ± 1.0 years, $P = 0.67$). Baseline serum GH levels were similar in both groups (PD: 2.3 ± 2.6 mU/L, MSA-P: 1.5 ± 1.3 mU/L, $P = 0.23$).

Serum GH levels after Clonidine increased progressively in PD after 15 min ($P = 0.001$), 30 min ($P = 0.001$), 45 min ($P = 0.001$) and 60 min ($P = 0.001$) but did not do so in MSA-P. After Clonidine, serum GH levels differed significantly between PD and MSA-P, at intervals after 15 and 30

min ($P = 0.01$ and $P = 0.01$) but not at 45 and 60 min ($P = 0.68$ and $P = 0.67$).

Conclusions: The GH response patterns are markedly different in PD and MSA. GH levels increase after clonidine progressively over an hour in PD unlike MSA-P where there is no response. CGHST can distinguish PD from MSA-P within 3 years of motor symptoms and thus aid in differentiation early in the course of these diseases.

P373

Movement disorders associated with fronto-temporal dementia with parkinsonism linked to chromosome 17 (FTDP-17)

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Parkinsonism can be due to pathological deposition of alpha-synuclein, tau, or polyglutamine. Recently, a group of inherited tauopathies caused by mutations in the tau gene (FTDP-17) have been described. The feature of the parkinsonism have been described in detail for the N279K mutation, but only for relatively few other mutations.

A 54-year-old lady developed asymmetric tremor, bradykinesia, and dysarthria at the age of 48 years and was referred to a Parkinson's disease (PD) clinic. Her tremor responded well to L-dopa but this medication led to deterioration in her behaviour and speech. She was initially apathetic and uninterested in day-to-day activities but later had become disinhibited, making frequent sexual comments and swearing. On examination, 6 years after disease onset, she had evidence of frontal lobe damage (utilization behaviour, applause sign, perseveration, poor category, and letter verbal fluency), parkinsonism (symmetric bradykinesia and rigidity, hypomimic facies) and features associated with progressive supranuclear palsy (PSP) (axial rigidity and slow hypometric vertical saccadic eye movements) (see accompanying videoclip). She had a strong family history of psychiatric illness and her mother died in psychiatric institutional care, having developed what was thought to be schizophrenia in her 50s. Her elder brother developed mental health problems and died at an early age. Her mother was born in the North Wales region of the UK. Molecular genetic analysis identified an exon 10 +16 tau mutation (common Welsh mutation).¹ FTDP-17 involves the combination of frontal dementia and some features of PD and PSP. It can present in a similar way to PD and a family history of psychiatric disease and genealogical links to North Wales may be clues as to the underlying diagnosis.

Reference

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P374

Multiple system atrophy genitourinary type: An emerging entity?

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Background: MSA patients present with Parkinsonism and cerebellar/autonomic dysfunction. Urogenital dysfunction occurs often within 1yr of motor symptoms.¹

Objective: If patients presenting to an urologist with storage symptoms and erectile dysfunction (ED)/motor dysfunction have MSA. Patients and methods: Nine patients (8 men, 1 woman) presenting to an urologist with storage symptoms and ED/motor disturbances were referred to a neurologist. They had been urodynamically evaluated and had detrusor overactivity with loss of inhibition in some.² A movement disorder specialist examined them. Screening cardiovascular autonomic function tests were performed and standard dopa-challenge testing was done if they had Parkinsonian signs. Based on clinical features and outcome of these tests patients were diagnosed as MSA using accepted diagnostic criteria.

Results: All 9 patients presented with Genito-urinary dysfunction. Six patients had non-dopa responsive parkinsonism. Two patients without parkinsonism had orthostatic hypotension and one of them had cerebellar signs. Two patients with parkinsonism had cerebellar signs. None of the parkinsonian patients had orthostatic hypotension or dopa-induced hypotension. Four patients were categorized as MSA-Parkinsonian type, 2 patients as MSA-Mixed type and 1 patient as MSA-Cerebellar type. Other

2 patients were normal on neurological examination. However, one of them had orthostatic hypotension on 60° tilt.

Conclusions: MSA patients may initially see an urologist for their genito-urinary dysfunction. Majority of them may have subtle neurologic symptoms(orthostatic hypotension, mild parkinsonism or cerebellar dysfunction) that may remain in the background and go unnoticed. Imaging may show cerebellar and/or brainstem atrophy suggestive of MSA. These patients could be classified as MSA-Genitourinary type. In patients presenting to urologists, andrologists or uro-gynaecologists with predominantly storage symptoms and/or erectile dysfunction, evaluation of motor problems may determine the possibility of MSA.

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P375

The pathological basis of disproportionate antecollis in multiple system atrophy

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Objective: To determine the clinicopathological correlation between disproportionate antecollis and important anatomical sites in multiple system atrophy (MSA).

Background: Focal dystonia in patients with MSA predominantly affects craniocervical muscles, and is often called "disproportionate antecollis."¹ This is characterized by severe neck flexion often with a tilt to one side.

Methods: We performed semiquantitative pathological analysis and clinical investigation of 100 pathologically confirmed MSA cases. In 24 anatomical areas of interest from both the striatonigral and olivopontocerebellar regions the severity of neuronal loss and gliosis as well as the frequency of glial (oligodendroglial) cytoplasmic inclusions were determined as previously described.²

Results: Complete clinical data were available for 80 of the 100 cases, and 20 of these had clinical documentation of disproportionate antecollis. In the globus pallidus internus, the neuronal cell loss was significantly more severe in MSA cases with disproportionate antecollis than in those without this sign ($P = 0.04$). In the putamen, caudate nucleus, and the substantia nigra, there was a trend for the pathological changes to be more severe in MSA cases with disproportionate antecollis while olivopontocerebellar pathology was unrelated.

Conclusions: Our results suggest that neurodegeneration in the substantia nigra and basal ganglia, especially the globus pallidus internus is associated with disproportionate antecollis in MSA.

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P376

Delayed onset of freezing of gait following the bilateral necrosis of the globus pallidus

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Object: To describe a patient with freezing of gait (FOG) following the necrosis of the globus pallidus (GP).

Background: Neural substrate of FOG remains controversial. A few reports were made to point out the importance of GP in the pathogenesis of FOG.

Methods: We followed up a patient with FOG.

Results: A 49-year-old man visited us because of gait disturbance. His gait disturbance insiduously started 3 years ago. He felt his feet glued to the ground. He frequently fell. He had a history of asphyxia 20 years ago. On neurologic examination, he was alert and well oriented. Cognitive function was normal. His gait was not short-stepped. FOG was mainly a start hesitation followed by the brief episodes of festination. His arm swing was decreased in the right side. Tremor and rigidity was absent. Brain MRI showed the bilateral necrosis of GP. Beta-CIT uptake was more markedly decreased in the putamen and in the left side. Dopaminergic medications were ineffective. Noradrenergic augmentation with amitriptyline and bupropion were partly effective.

Conclusions: FOG in our patient might be related to both subclinical parkinsonism and the necrosis of GP. Nondopaminergic medications might have direct effects on the brainstem bypassing the basal ganglia.

P377

Deep brain stimulation of subthalamic nucleus can improve parkinsonism symptoms in sinemet non-responsive patients

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Objective: To test the efficacy of deep brain stimulation (DBS) of the subthalamic nucleus (STN) in the surgical treatment of patients who are unresponsive to anti-parkinsonism medications using Unified Parkinson's Disease (PD) Rating Scale (UPDRS).

Background: A good response to levodopa is a major inclusion criterion while lack thereof is a contraindication to DBS. However, there is a subset of Sinemet non-responsive patients who present with rigidity, bradykinesia, postural instability, and resting tremor, all the symptoms that are highly responsive to DBS. We hypothesize that such patients might benefit from DBS of the STN.

Methods: Four patients with severe symptoms of parkinsonism (rigidity, bradykinesia, postural instability, tremor) and no or marginal response to anti-parkinsonism medications (Sinemet, Requip, Permax, Comtan, Amantadine, Pergolide, etc.) were operated. All patients (2 male and 2 female) suffered from advanced refractory Parkinsonism. Mean patients age was 65.3, ranging from 41 to 69.

Parkinsonism duration was from 5 to 22 years. Each patient signed an informed consent letter that included a clause about the widely accepted rule that Sinemet non-responsive parkinsonism is a contraindication for deep brain stimulation. The STN coordinates were defined using T2-weighted STIR sequences; the AC-PC was defined using 3D volume acquisition (SPGR/12). The Z coordinate (4 to 6 mm below the AC-PC line) was determined on the MRI slice that contains the optic tracks, mammillary bodies, red nuclei, and STN. Intraoperative microelectrode recording and macrostimulation verified the X, Y, and Z coordinates.

Results: All four patients received bilateral electrode implants to the subthalamic nucleus that has resulted in near complete symptom resolution with stimulation from 1 to 4 V. Twelve months after surgery, DBS-STN improved UPDRS (part 3) scores by 69% to 79% in all four patients.

Conclusions: DBS-STN can be successful in a subset of L-Dopa non-responsive patients. We are currently exploring criteria, which might indicate those non-responsive patients who would respond to STN-DBS.

P378

Hemiparkinsonism and facial dyskinesia in a patient with a contralateral mesencephalic cyst

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Objective: To report a case of a mesencephalic cyst presenting as hemiparkinsonism and facial dyskinesias.

Background: Space-occupying lesions of the midbrain have been recognized as a rare etiology of secondary parkinsonism. This is only the sixth case demonstrating this association.

Methods: Case report.

Results: A 71-year-old right-handed man presented with a progressive left-side tremor over the preceding 3 years and bilateral facial dyskinesias. The tremor occurred only at rest, without a postural component. He

complained of involuntary bilateral facial grimacing and eye blinking that had been stable for the past 20 years, as well as recent falls. On examination, the patient had no orthostasis. His mental status was normal. He had significantly diminished upgaze and bilateral orofacial dyskinesias. There was an intermittent 5 Hz rest tremor of the left hand with a less severe left foot tremor. He had no rigidity and normal postural reflexes. There was a reduced left arm swing. The rest of his examination was normal. MRI of the brain revealed a multilobulated cystic lesion involving the right mid-brain including the cerebral peduncle, extending to the right upper pons and thalamus. MR spectroscopy was not consistent with tumor. Levodopa/carbidopa resulted in mild improvement in the left-side tremor, but no change in facial grimacing. He underwent stereotactic drainage of the cystic lesion. Postoperative MRI showed no change in the size of the lesion. No clinical improvement occurred postoperatively.

Conclusions: This case demonstrates hemiparkinsonism associated with a contralateral cystic lesion of the mesencephalon that initially presented as bilateral facial dyskinesias. A videotape will be shown.

P379

Parkinsonism induced by bupropion

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Objective: To present a case of parkinsonism induced by bupropion.

Background: Bupropion is an antidepressive drug which interferes with serotonin and adrenaline uptake and has low affinity on α -adrenergic receptors. Its effect on dopaminergic neurotransmission is not clear.

Methods: A 49-year-old man who used to smoke 40 cigarettes per day was started on treatment with bupropion hydrochloride (300 mg/d) for abandoning the smoking habit. Fifteen days after the onset of this treatment the patient began to experience cervical stiffness, loss of facial expression, slowness of movements, hypophonic voice, loss of arms movements while walking, and shortness of the strides. On examination a bilateral and symmetric akinetic-rigid syndrome was observed, in addition to mild oro-lingual dyskinesias. A brain MRI and a brain SPECT study with ^{123}I -Ioflupane were normal.

Results: Bupropion hydrochloride was stopped, but the parkinsonian symptoms were still present 1 month later. The patient was then treated with cabergoline (2 mg/d) with progressive improvement until complete disappearance of parkinsonism. He remains asymptomatic 6 months after discontinuing cabergoline.

Conclusions: We report on a patient who experienced a parkinsonian syndrome after a short exposure to bupropion. The parkinsonian symptoms disappeared after discontinuing this drug. The SPECT with ^{123}I -Ioflupane was normal suggesting that bupropion does not modify DAT and that the patient has not presymptomatic Parkinson's disease. Bupropion might produce a reversible blockade of postsynaptic dopamine receptors. This compound should be included in the list of drugs capable of inducing a parkinsonian syndrome.

P380

Gait and balance assessment in parkinsonian disorders

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Objective: To characterize gait patterns in Parkinson's disease (PD), progressive supranuclear palsy (PSP), and vascular parkinsonism (VP), and to correlate phenomenology with corresponding diagnosis.

Background: In contrast to the classical short shuffling steps, narrow base and flexed knees typical of PD, PSP patients pivot, and have a stiff, broad-based gait with extended knees. VP has a broad-based gait and lower body parkinsonism.

Methods: Subjects were patients and spouses recruited from the Movement Disorders Clinic. Modified GABS and Tinetti scales were used for gait assessment.¹ Videos from waist down (so as not to reveal diagnostic clues such as hand tremor) were randomized. Gait phenomenology was rated by two investigators blinded to patients' diagnoses. A diagnostic algorithm based on characteristic gait patterns was formulated and tested against known diagnoses to determine its predictive sensitivity (SE) and

specificity (SP). Results: 45 subjects (62% males) with mean age 71.5 ± 9.7 years and symptom duration 8.3 ± 6.8 years included controls (8), PD (19), VP (9) and PSP (9). Raters' scores were consistent for both gait scales (Spearman rho = 0.78–0.91, $P < 0.0001$), but Rater 2 attributed greater severity on the Tinetti scale ($P < 0.0001$). Moderate accuracy (SE = 100%; SP = 76–81%; K = 0.53–0.60, $P < 0.0001$) and intra-rater reliability (K = 0.61, $P < 0.0001$) obtained by the normal gait algorithm. Despite fair inter-rater reliability (K = 0.39, $P < 0.02$), the PD gait algorithm for either rater did not produce the correct diagnosis (SE = 63–74%; SP = 42–46%; K = 0.05–0.19, $P > 0.05$). The VP gait algorithm was generally accurate (SE = 67–100%; SP = 61–69%; K = 0.27–0.39, $P = 0.06$ –0.001), while the algorithm for PSP yielded absolute specificity (SP = 100%), but poor sensitivity (SE = 11–22%, K = 0.17–0.31, $P = 0.2$ –0.04). The primary global impression of both raters yielded high concordance (K = 0.26–0.4, $P < 0.004$) across controls (100%), PD (68–74%), VP (11%), and PSP (11–33%).

Conclusions: Although global impressions among movement disorders specialists appeared more accurate in differentiating gait patterns, our algorithmic method could potentially identify gait phenomenology specific to various parkinsonian disorders. Its utility and strength is the standardization it would provide in future gait protocols.

References

1. J Neurol Sci.2004;217:89.

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Gait assessment in parkinsonism, dementia, and normal ageing

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Objective: To compare gait parameters in normal population and degenerative diseases at baseline and when doing mental tasks.

Background: Previous studies have shown gait deterioration in demented patients when they are doing mental tasks. We have now used the same methodology but including parkinsonian patients with and without dementia.

Methods: we studied 39 patients with idiopathic parkinsonism (average age = 62 ± 13), 16 patients with degenerative dementia without parkinsonism (average age = 73 ± 6), and 38 normal people (average age = 59 ± 11). Subjects were asked to walk 12 meters and then to walk the same distance whilst doing mental tasks. Total time, steps, and motor blocks were assessed comparing the three groups.

Results: At baseline (walking without mental task) demented and parkinsonian patients were slower than normal ones ($P = 0.2$ and $P = 0.4$, respectively).

The three populations studied expended a significant longest walking time when doing mental tasks ($P = 0.01$). Demented patients had a significant prolonged walking time when doing mental activities in comparison with normal ones ($P = 0.01$), but parkinsonian patients did not ($P = 0.5$).

Conclusions: Cognitive activities are able to modify gait speed in normal, demented, and parkinsonian patients. This effect is probably mediated by attention demands during gait, imposed by simple mental tasks. These gait modifications tend to be marked in demented patients suggesting that mental condition rather than motor capabilities are challenged with this test. Risk of falling could not be predicted with this method either in demented or parkinsonian patients.

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Extrapyramidal symptoms in a group of Italian dental laboratory technicians

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Many epidemiological studies and case-report show an association between exposure to neurotoxins and parkinsonism. In the clinical practice the identification of patients with suspected toxic etiology is linked to collect an accurate occupational history.

The clinical history of a juvenile parkinsonian patient with a slow progression and a persistent asymmetry symptomatology after 6 years of duration disease induce an accurate evaluation of his occupational history.

This patient works as a dental laboratory technician in a public school and has been probably exposed to mercury sulphate for many years. We have visited 14 men dental laboratory technicians among 27 workers of this public school (age mean 48.8 ± 5.9 years) and have identified six subjects with a mild postural tremor, bradykinesia and rigidity. However, for each subject it is not possible actually diagnose a parkinsonism. On the contrary the high prevalence of parkinsonian signs in a small group of juvenile workers of same occupational environment is not frequent and should be evaluated carefully. We believe that the evaluation of possible association between exposure to neurotoxins among dental laboratory technicians and onset of p extrapyramidal symptomatology should be considered in the clinical practice.

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Valvular heart disease in Parkinson's disease versus controls—An echocardiographic study

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Objective: To assess the frequency of valvular heart disease (VHD) in Parkinson's Disease (PD) patients treated with Pergolide or Cabergoline and compare findings to those treated with Pramipexole or Ropinirole, as well as to a control group.

Background: Recently there has been growing concern about the potential of certain Dopamine Agonists (DA) used in the treatment of PD to induce VHD.

Initial reports were in patients treated with Bromocriptine, but most cases published since then had been on treatment with Pergolide.

Methods: PD patients taking Pergolide (PD/PERG) or Cabergoline (PD/CAB), Pramipexole (PD/PXP) or Ropinirole (PD/ROP) for a minimum of 1 year without previous exposure to ergot-DA for more than 6 months were assessed by routine echocardiography.

Patients exposed to several ergot-DA (minimum >6 months including Cabergoline, Pergolide and Bromocriptine) were analyzed as "mixed" ergot-group (PD/MIX). Age-matched general neurology patients served as controls.

Transthoracic echocardiographic studies were performed following standardized protocols and reports were reviewed for valvular regurgitation (VR) grade II–III.

Results: There were 33 patients in the non-ergot (NE) group (25 PD/PXP, 8 PD/ROP), 53 in the ergot group (29 PD/PERG, 14 PD/CAB, 10 PD/MIX), and 51 in the control group.

31% of PD/PERG patients had VR II–III vs. 14% of controls ($P = 0.06$), while 43% of PD/CAB patients showed VR II–III vs. 14% of controls ($P = 0.01$). PD/MIX patients also had higher prevalences of VR II–III than controls (40% vs. 14%, $P = 0.04$).

VR II–III prevalences did not differ between NE and controls (10% vs. 14%, $P = 0.52$), while PD/CAB and PD/PERG patients showed higher prevalences than NE patients (43% vs. 10%, $P = 0.007$ and 31% vs. 10%, $P = 0.02$).

Clear-cut fibrotic changes with leaflet thickening and/or retraction were evident only in 2 cases, both on Pergolide.

Conclusions: In our study, treatment with Pergolide and Cabergoline was associated with higher prevalences of valvular regurgitation compared to age-matched controls, while there was no increase in valvular regurgitation in patients treated with non-ergot DA. The mechanisms underlying this difference are unclear, since fibrotic changes described as a reaction to ergot agonists were seen in only two cases on pergolide.