Movement disorders 4

EP4216

Switching L-dopa therapy from “pulsatile” to “pulse” reduces wearing-off and dyskinesia in complicated Parkinson’s disease. A waking day monitoring study

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Introduction: Conventional modality of L-dopa administration consisting in intermittent multiple daily small doses (the so-called “pulsatile” treatment modality) may determine an intermittent stimulation of dopamine receptors leading to motor fluctuations. A therapeutic regimen consisting in standard oral doses at specific interdoses intervals exploiting the long-duration response to the drug and designated as oral “pulse” L-dopa therapy could instead result in a more physiological and tonic stimulation of dopamine receptors, reducing motor fluctuations and dyskinesia.

Methods: Thirty-four Parkinson’s disease (PD) patients with motor complications (N=21 fluctuating; N=13 dyskinetic) underwent two consecutive standardized waking day motor status evaluations using UPDRS-ME and the Abnormal Involuntary Movement Scale (AIMS) after switching L-dopa administration from “pulsatile” to “pulse” modality. To quantify predictable motor fluctuations, a Wearing-Off Index (WOI) was computed based on changes in L-dopa response magnitude between the two assessments.

Results: We found a significant reduction in number of daily doses while an increase in average single dose between the two assessments, with no differences in cumulative daily dosage of L-dopa. Maximal AIMS score detected during the motor status monitoring was significantly lower at the second assessment. In fluctuating patients, there was a significant reduction in UPDRS-ME average score as well as in WOI. In dyskinetic patients, there was a significant reduction in average and maximal AIMS scores with no changes in average and maximal UPDRS-ME scores.

Conclusions: Switching L-dopa therapy from “pulsatile” to “pulse” reduces wearing-off and dyskinesia in complicated PD.

Disclosure: Nothing to disclose

EP4217

Chorea in neurometabolic diseases

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Introduction: Neurometabolic diseases (NMD) are a heterogeneous group of genetic disorders which could involve the basal ganglia. Chorea is reported as a sign of a complex clinical picture in NMD. We report on 13 children with chorea due to NMD and describe clinical features, imaging, aetiologies and treatment.

Methods: We conducted a retrospective study over a 4-year period (from 2009 to 2013) including all children diagnosed with chorea due to NMD. Clinical features, videos of patients, imaging, and treatment were analyzed.

Results: Thirteen children over 70 patients with chorea were included (9 boys and 4 girls, mean age: 8.6 years, mean age of onset: 3.8 years). Consanguinity rate was 69.2%. Family history showed 38.5% of similar cases. Associated movement disorders to chorea were noted: dystonia (53.8%), myoclonus (46.2%) tremor and stereotypes (23.1%). Brain MRI was performed in all patients and showed basal ganglia abnormalities in 33%. Main NMD observed were mitochondriopathies and glutaric aciduria type I. 46.2% of our patients were treated with neuroleptics, with good improvement.

Conclusions: The high rate of consanguinity and the presence of familial chorea in our study suggest a genetic origin. The frequency of chorea in NMD could be explained by the vulnerability of basal ganglia to metabolic disturbance. NMD should be evoked in every child with chorea belonging to a consanguineous family.

Disclosure: Nothing to disclose
EP4218

An autopsy case of the homozygous dentatorubral-pallidoluysian atrophy

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Dentatorubral-pallidoluysian atrophy (DRPLA) is a hereditary neurodegenerative disease caused by an expansion of the CAG repeat in the DRPLA gene. The size of expanded CAG repeats is inversely correlated with the onset age and also associated with clinical phenotype. It was reported that expanded polyglutamate stretches are more widely and densely distributed in the central nervous system in the juvenile-onset than adult-onset cases. Here we report a juvenile-onset case of the homozygous DRPLA. This Japanese male initially developed ataxic gait and choreoathetosis at the age of 17 years. These symptoms gradually worsened, and epilepsy and related psychotic features, personality change, and dementia subsequently occurred. His parents were first cousins. His four siblings developed intellectual deterioration and epileptic seizures, and all of them died at age 12-13. Genetic analysis disclosed a homozygous state of small expansions (57 repeats) of his CAG repeats in the DRPLA gene, although his onset age was young. He died of pneumonia at age 45. Pathologically, many nuclei diffusely labeled by an anti-atrophin-1 antibody, as well as those labeled by 1C2, were observed in the basal ganglia, cerebellum, and spinal cord, including the dentatorubral and pallidoluysian system. In addition, these labeled nuclei were frequently found in the neocortex, hippocampus, and subiculum, which distribution was similar to that observed in young-onset heterozygous cases having long expansion of CAG repeats. Given these findings, homozygous state of expanded CAG repeats may be associated with the earlier age at onset and more severe involvement of extra-dentatorubral and pallidoluysian system.

Disclosure: Nothing to disclose

EP4219

Longitudinal outcomes from the international disease registry for Niemann-Pick disease type C (NP-C)

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Introduction: NP-C is a progressive neurological disease where progression varies depending on age at onset. We report progression of disability in patients continuously treated with miglustat for ≥1 year.

Methods: The NPC Registry is a prospective observational cohort of NP-C patients. Enrolled patients who received ≥1 year of continuous miglustat therapy (for ≥90% of the observation period, with no single treatment interruption >28 days) were included in this analysis. Disability was measured using a scale rating the four domains, ambulation, manipulation, language and swallowing from 0 (normal) to 1 (worst). Patients were categorised as ‘improved/stable’ if ≥3/4 domain scores were lower/unchanged, and as ‘progressed’ if <3 scores were lower/unchanged between enrolment and last follow-up visit.

Results: In total, 283 patients were enrolled between September 2009 and October 2013; 92 received continuous miglustat therapy. The mean (range) miglustat exposure from enrolment to last follow-up was 2.0 (1.0-3.7) years. Among 84 evaluable patients, 9 (11%) had early-infantile (<2 years), 27 (32%) had late-infantile (2 to <6 years), 30 (36%) had juvenile (6 to <15 years) and 18 (21%) had adolescent/adult (≥15 years) onset of neurological manifestations. The overall mean (95%CI) composite disability score was 0.37 (0.32,0.42) at enrolment and 0.44 (0.38,0.50) at last follow-up. In total 55/81 (68%) miglustat-treated patients were ‘improved/stable’: 33% of early-infantile, 50% of late-infantile, 79% of juvenile, and 94% of adolescent/adult-onset patients.

Conclusions: Disability status was improved/stable in the majority of patients who received continuous miglustat therapy for an average period of 2 years.

Disclosure: This Registry is sponsored by Actelion Pharmaceuticals Ltd. MP has received consulting fees, honoraria and research grants from Actelion Pharmaceuticals Ltd.
EP4220

Apopomorphine responsivity in hemiparkinson hemiatrophy syndrome: a case report

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Introduction: The Hemiparkinsonism-Hemiatrophy-Syndrome (HPHA) is hallmarked by hemiatrophy and ipsilateral parkinsonian symptoms (rigidity, tremor and bradykinesia) and often combined with dystonia.

Methods: We report the case of a 54-year-old man of Bosnian ancestry, who suffered from head injury at the age of 7, followed by atrophy of his right upper and lower limb. The hemiatrophy began at the first dorsal interosseous muscle at the age of 21. 27 years later, at the age of 48, tremor occurred at the right upper extremity, accompanied by dystonia of digit V and cramps in the right foot. His mother suffered from tremor, but there was no evidence of Parkinson’s Disease. Apart from his mother, there were no neurological disorders in his family.

Results: The neurological examination showed right-sided limb atrophy associated with moderately severe bradykinesia and rigidity (MDS UPDRS III: 42; H&Y: 3). The finger-nose test was dysmetric and there was rest and kinetic tremor in addition to dystonic posturing of the right upper limb. Power of the right upper and lower extremity was decreased. MRI demonstrated an increased apparent diffusion coefficient as well as an enhanced iron content in the substantia nigra. His response to oral L-Dopa treatment was poor, therefore, he received an Apomorphine-pump and pen, which improved tremor and bradykinesia (MDS UPDRS III: 30; H&Y: 2).

Conclusions: History, clinical findings and MRI results are consistent with HPHA. Our case report demonstrates that dopaminergic responsiveness may be achieved by invasive continuous dopaminergic stimulation.

Disclosure: Nothing to disclose

EP4221

Opicapone pharmacokinetics and pharmacodynamics comparison between healthy Japanese and matched Caucasian subjects

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Introduction: Opicapone (OPC) is a novel third generation COMT inhibitor endowed with an exceptionally high binding affinity, which translates into a slow complex dissociation rate constant and a long duration of action.

Objectives: Compare the pharmacokinetics and pharmacodynamics (COMT-activity) of OPC between healthy Japanese and matched (age±5 years, gender and body-mass-index±4kg/m²) Caucasian subjects.

Methods: Single-centre, randomized, double-blind, parallel, placebo-controlled, multiple-ascending-dose study. Three sequential groups of up to 38 (19-Japanese plus 19-Caucasian) subjects each were randomized to receive once-daily, for 10-days, 5, 25 and 50-mg OPC or Placebo (14:5 ratio per group). Geometric mean ratios (GMR) and corresponding 95% confidence intervals (95%CI) for main parameters were calculated and compared to [80%-125%] interval.

Results: No statistical differences were found for OPC pharmacokinetics (tmax, Cmax and AUC) and pharmacodynamics (tEmax, Emax and AUEC) when different doses of OPC were compared between populations. Point-estimates (PEs) of pharmacokinetics GMR (95%CI) following last-dose regimen were as follows: Cmax 123 (78-195), 134 (95-189) and 120 (91-160); AUC0-t 136 (94-197), 118 (89-157) and 119 (88-161) for 5, 25 and 50-mg OPC, respectively. PEs of pharmacodynamics GMR (95%CI) following last-dose regimen were as follows: Emax 96 (80-116), 96 (90-102) and 98 (94-101); AUEC: 110 (65-175) and 112 (88-153) and 95 (64-140) for 5, 25 and 50-mg OPC respectively.

Conclusion: Only minimal differences were noted that were deemed not to be statistically significant between the Japanese and Caucasian population. Thus, ethnicity had no significant impact on the pharmacokinetics and pharmacodynamics of OPC in the conditions of the study.

Disclosure: Nothing to disclose
EP4222

Positive effects of erythropoietin on a rat model of Parkinson's disease

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Introduction: Erythropoietin (EPO) is a peptide hormone synthesized from kidneys. This hormone is also produced in brain, liver, testis, lung, and spleen. Aim of this study represented is to investigate effects of EPO, whose neuroprotective effects were previously reported, in the rat model of Parkinson’s Disease (PD).

Methods: Eighteen Sprague-Dawley adult male rats were included in the study and were divided into 3 groups (n=6). Rotenone+Dimethyl sulfoxide (DMSO) was stereotactically injected to the left substantia nigra compacta and ventral tegmental area of the group 1 and group 2. Only DMSO was applied to the same localization of the third group as a sham group. Rotation test was applied to rats awaited for 10 days by administering intraperitoneally apomorphine. Rats having continuous rotation in the same direction 7 times per minute in apomorphine-induced rotation test (AIRT) were considered as PD. 2,500 IU/kg EPO was applied to Group 1, and isotonic saline was applied to Group 2 for 28 days. Then apomorphine-induced rotation numbers for 10 minutes were recorded. Malondialdehyde levels in plasma and thyrosine hydroxylase (THA) (dopamine degradation product) levels in brain of the rats were examined.

Results: AIRT values and plasma malondialdehyde levels of the group 1 were statistically significantly decreased in comparison with the group 2. THA levels were higher in the group 1 compared to group 2 (p<0.005).

Conclusions: In this study, EPO was detected to have positive effects on rat model of PD. This result may provide an insight to new treatment alternatives for PD treatment.

Disclosure: Nothing to disclose

EP4223

Apathy in early Parkinson's disease

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Introduction: Apathy is a common behavioural problem in Parkinson’s disease (PD), with severe impact on quality of life. Apathy in early PD has been linked to ventral striatum and mesolimbic dopaminergic denervation, but involvement of noradrenergic and serotonergic metabolism has also been suspected.

Objective: We examined the frequency and clinical characteristics of apathy in 113 nondemented patients with newly diagnosed PD Hoehn and Yahr (HY) stage 1 and 137 control subjects matched for age, sex and education level.

Methods: All participants underwent psychiatric investigation with the Starkstein’s Apathy Scale (AS), and the 17-item Hamilton Depression Rating Scale (HDRS-17), Neuropsychiatric Inventory assessment (NPI), motor scoring with HY staging, and the Unified Parkinson’s Disease Rating Scale (UPDRS); and cognitive screening with the The Addenbrooke’s Cognitive Examination Revised (ACE-R) on the same day. Apathy was diagnosed based on proposed consensus criteria.

Results: Apathy was found in 41.2% of the PD patients, of whom 31.2% had significant depressive symptoms. Apathy was significantly associated with male gender, more severe motor symptoms and higher depression scores, but was not associated with ACE-R scores. When excluding patients with significant depressive symptoms, apathy remained significantly associated with motor severity.

Conclusion: Apathy remains a main psychiatric symptom even in early PD. Association between apathy and motor severity suggests a common underlying pathophysiological mechanism.

Disclosure: Nothing to disclose
**EP4224**

**[¹²³I]FP-CIT SPECT (DaTSCAN) in unclear parkinsonism: a useful tool to differentiate between Parkinson’s disease and vascular or drug-induced parkinsonism**

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**Introduction:** We systematically reviewed the utility of dopamine system imaging [¹²³I]FP-CIT SPECT (DaTSCAN) in unclear parkinsonism, namely in the differential diagnosis between idiopathic Parkinson’s disease (PD) and vascular (VP) or drug-induced (DIP) parkinsonism.

**Methods:** We searched MEDLINE and CENTRAL to identify studies reporting enough data to determine accuracy measure (sensitivity, specificity, diagnostic Odds Ratio - DOR, positive and negative likelihood ratios - pLR, nLR) of [¹²³I]FP-CIT SPECT in differentiating between PD and VP/DIP in unclear parkinsonism. The methodological quality of studies was evaluated with QUADAS.

**Results:** Five studies were included. Pooled accuracy measures in the differential diagnosis between PD and VP were: sensitivity: 86.2% (95% CI 81.3 - 90.1%); specificity 82.9% (95% CI 67.9 - 92.8%); pLR 4.813 (95% CI 1.523 - 15.211); nLR 0.190 (95% CI 0.139 - 0.259); DORs 28.528 (95% CI 8.450 - 96.309). Pooled accuracy measures in the differential diagnosis between PD and DIP were: sensitivity 86.2% (95% CI 81.3 - 90.1%); specificity 93.8% (95% CI 69.8 - 99.8%); pLR 5.366 (95% CI 1.913 - 15.050); nLR 0.178 (95% CI 0.125 - 0.253); DORs 39.638 (10.380 - 151.36).

**Conclusions:** [¹²³I]FP-CIT SPECT might accurately differentiate between early PD and VP/DIP in patients with unclear parkinsonism. However, all the studies conducted show methodological limits, which prevent to draw conclusions on the real accuracy of [¹²³I]FP-CIT SPECT. Further studies with higher methodological quality and homogeneous diagnostic criteria of VP and DIP are needed to definitely evaluate the diagnostic utility of [¹²³I]FP-CIT SPECT in differentiating between PD and VP or DIP.

**Disclosure:** Nothing to disclose

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**EP4225**

**Parkinsonism associated with liver cirrhosis – a case report**

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**Introduction:** We present a case report of a patient with cirrhosis and secondary parkinsonism. The patient is a 58-year-old male who is complaining of clumsiness of the movements of his right arm, general slowness of his body movements, mild changes in his gait. The symptoms had relatively rapid progression over months. The patient has had chronic C Hepatitis and liver cirrhosis with portal hypertension for several years.

**Methods:** We have used detailed neurological examination, EMG, MRI, general blood tests plus ammonia, manganese, copper and ceruloplasmin levels in blood.

**Results:** We found hypomimia, bradykinesia, mild rigidity in his right arm, slowed walk with decreased synkinesias of the right arm on clinical examination, MRI data pointing towards acquired hepatocerebral degeneration, increased levels of ammonia and manganese and normal levels of copper and ceruloplasmin in blood.

**Conclusions:** We concluded that the extrapyramidal symptoms in our patient were secondary to liver impairment. This clinical case shows the importance of considering acquired hepatocerebral degeneration in the differential diagnosis when managing patients with parkinsonism.

**Disclosure:** Nothing to disclose
EP4226

Dopa-responsive dystonia presenting with spastic dysphonia

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Introduction: Dopa-Responsive Dystonia (DRD) is a broad term used to describe forms of dystonia that respond to levodopa.

Methods: A 50-year-old female visited the Outpatient Clinic of Neurogenetics of General Hospital Papageorgiou with a long history of gait disorders with childhood onset and progressive deterioration. She had started to walk at the age of 20 months but never actually managed to run properly. By the age of 4 she had been presenting with a dystonic right leg and during childhood she recalled tiptoe walking. Progressively during puberty and adulthood she established writer’s cramp and right torticollis. The most prominent feature, however, was spasmodic dysphonia present the last few months. Family history was free with the exception of cervical muscle cramps of the mother.

Results: On the clinical suspicion of DRD levodopa was initiated. Genetic test revealed a GCH1 mutation. Sequencing analysis of the GCH1 gene revealed an Arg88Trp variation that was reported as pathogenic in GCH1 variation viewer. Due to the spectacular response of dysphonia to levodopa, it was titrated up to 200mgx3. 2 months later, dysphonia was dramatically improved however the rest of the symptoms were fairly ameliorated.

Conclusions: Clinical manifestations of DRD cover a broad spectrum of signs and symptoms from generalized, severe dystonia to subtle signs only seen upon induction. This patient presented with a rather typical onset and progression of the disease apart from spasmodic dysphonia which is relatively rare in DRD. The elective response of one symptom only to dopaminergic therapy is rather unusual.

Disclosure: Nothing to disclose

EP4227

Lewy body dementia: a three-year clinical follow up study

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Few studies systematically investigated the relationships between the symptoms and the clinical course of DLB with a long term follow up. Aim of this study is to analyze a broad pattern of clinical aspects of the disease in patients affected by DLB, with a 3 years follow up. We selected 77 patients with DLB probable. We retrospectively analyzed the age of onset, the prevalent type of onset, motor disease severity, the acute and chronic response to levodopa (LD) and the LEDD. MMSE, cognitive fluctuations (CFs), visual hallucinations (VHs), therapies with cholinesterase inhibitors or Memantine and neuroleptic treatments were also investigated. 47 patients had a 3 years follow up. The most common onset type was a mixed phenotype, followed by the motor and cognitive phenotype. A positive LD response was present in 40.3%. In the 3 years follow up, all tremor dominant patients converted to PIGD. An earlier onset was associated to a prevalent PIGD. PIGD was associated to a higher occurrence of VHs, higher worsening of rigid/akinetic subscores at UPDRS part III and worsening of MMSE during 3 years. VHs occurred at baseline in 30.4% and were associated to a more prevalent PIGD and younger disease onset and with a faster MMSE and rigid akinetic UPDRS subscores decline. The presence of VHs was associated to CFs. We found significant associations between symptoms and if confirmed by larger studies, some of them could represent possible predictors of follow up outcome.

Disclosure: Nothing to disclose
EP4228

Postural control changes in visual height intolerance: body sway and anti-gravity muscle activity

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Introduction: Visual height intolerance (vHI) occurs when a visual stimulus causes the apprehension of losing balance and falling. Although vHI affects almost one-third of the general population and has relevant consequences on the quality of life, a quantitative assessment of physiological alterations that may trigger postural imbalance in vHI is missing.

Methods: VHI-related changes in postural control were assessed by center-of-pressure displacements and electromyographic recordings of selected leg, arm, and neck muscles in 16 subjects with vHI while standing at heights on an emergency balcony vs. standing in the laboratory at ground level. Characteristics of open- and closed-loop postural control were analyzed. Body sway and muscle activity parameters were correlated with the subjective estimates of fear at heights.

Results: During height exposure,
1. open-loop control was disturbed by a higher diffusion activity (p<0.001) and
2. the sensory feedback threshold for closed-loop control was lowered (p<0.010).

Altered postural control was predominantly associated with increased co-contraction of leg muscles. Body sway and leg and neck muscle co-contraction correlated with the severity of subjective anxiety (p<0.050). Alterations in postural control diminished if there were nearby stationary contrasts in the visual surrounding or if subjects stood with eyes closed. The performance of a cognitive dual task also improved impaired balance.

Conclusions: Visual heights have two behavioral effects in susceptibles: a change occurs in
1. open- and closed-loop postural control strategy and
2. co-contraction of anti-gravity leg and neck muscles, both of which depend on the severity of evoked fear at heights.

Disclosure: Nothing to disclose

EP4229

Quality of life in patients receiving combination therapy with pramipexole

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Introduction: Non-motor disorders such as depression, anxiety, cognitive impairment, pain, sleep disorders, etc. have a great role in disability in patients with Parkinson’s disease (PD). They lead to the restriction in all spheres of patient’s life consistently reducing its quality. Rational therapy is able to delay the offensive some of these symptoms and ensure the best quality of life.

Methods: 38 patients with PD (22 women and 16 men) aged 37 to 76 years (mean age was 64.7±9.0), average duration of disease was 7.18±4.2 years. The disease stage at Hyun and Yar scale was: II-29% of patients, III-68.4%, IV-2.6%. There were such forms of the disease like tremor-in 7.9%, akinetic-rigid-44.7%, mixed-47.4%. All patients receiving the combination therapy were divided into groups:
1. 8 people who did not receive therapy with Pramipexole,
2. 13 people who received pramipexole 1.5mg/day and less,
3. 17 people who received Pramipexole at a dose of more than 1.5mg/day.

Quality of life was determined by questionnaire MOS Shot-form 36-Item (MOS SF-36).

Results: Patients in II group had the best performance in Role-Physical Functioning, Bodily pain, Vitality, Social Functioning, Mental Health, Physical health according to the SF-36. The greatest difference between the groups was in Role-Emotional, due to the emotional state: I- 1.0±35.4; II-64.1±46.1; III-22.3±28.2 points (p<0.01). There was no statistically significant difference between groups I and II in the life quality assessing by the overall health (p>0.05).

Conclusions: Using the dopamine receptor agonist Pramipexole in the average therapeutic dose greatly improves the quality of life of PD patients.

Disclosure: Nothing to disclose