

# Atypical Parkinsonian Syndromes – an International Symposium on Neurodegenerative Diseases

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## 1. The Concept of Vascular Parkinsonism

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The presence of parkinsonian symptoms with concomitant cerebrovascular lesions is often reported as vascular parkinsonism (VP) and refers primarily to patients with gait difficulties, lower body symmetrical bradykinesia, and lack of resting tremor. However, neuropathology studies have demonstrated that clinical presentation of VP is heterogeneous and there is often overlap with Parkinson's disease (PD) particularly if patients benefit from dopaminergic medications. Indeed, similarly to elderly control subjects, brain vascular lesions may be present in almost 25% of PD patients but their contribution to clinical manifestations is unknown.

In a recent study we explored the relationship between clinical features, brain MRI as well as in vivo striatal dopamine nerve terminal status in a large cohort of elderly consecutive patients with vascular lesions recruited at multiple movement disorder centers in Italy.

Cerebral vascular disease was associated with increased disease severity of parkinsonism and negatively affected response to chronic levodopa therapy. There was a significant association between disease severity (HY stage) and cerebral vascular lesions, particularly those located in periventricular and hemispheric white matter or infratentorial areas (i.e. brainstem and/or cerebellum) in patients with normal striatal DAT binding. Finding of normal uptake was associated with no benefit from medications in over 90% of subjects.

Overall multiple cerebral vascular lesions modify clinical presentation and severity in patients with parkinsonism and this is underlined by specific risk factors primarily hypertension. Striatal DAT assessment is helpful in identifying patients where therapy benefit is less likely.

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## 2. Continuous Duodenal Levodopa Delivery (DuoDopa) for the Management of Advanced Parkinson's Disease Patients

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Long-term L-dopa therapy is associated with the development of motor fluctuations and dyskinesias in the majority of patients with Parkinson's disease (PD). Dyskinesias are likely to result from the interaction between the primary degenerative process and the chronic exposure to pulsatile oral L-dopa therapy.

All studies comparing early L-dopa vs. dopamine agonist early therapy indicate that initiation with agonists is associated with a reduced risk for motor complications – in particular dyskinesias – possibly because agonists longer half-lives provide continuous dopaminergic delivery.

In advanced patients switching from a pulsatile to continuous dopaminergic delivery avoids peaks and troughs in L-dopa plasma and may also widen the therapeutic window. Currently this can be accomplished only with subcutaneous apomorphine or duodenal levodopa infusions. Particularly duodenal L-dopa infusion is promising because continuous delivery with an optimized dose can be ensured and peripheral L-dopa can be kept stable within the patient's individual therapeutic window allowing replacement all oral medications.

The levodopa is administered via a permanent catheter implanted into the duodenum by percutaneous endoscopic gastrostomy (PEG) under local anaesthetic. Administration of the drug is controlled by a pump with an adjustable infusion rate allowing fine-tuned titration, individual adaptation of dose and also allows administration of extra doses (if needed).

Our experience indicates that a satisfactory therapeutic window can be achieved and maintained for several months in advanced PD patients. This is associated with improved motor fluctuations and reduced disabling dyskinesia, resulting in significant benefit in quality of life and several non-motor domains.

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## 3. Spinocerebellar Ataxias

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Spinocerebellar ataxias (SCA) can be divided into three categories: Autosomal dominant SCA, autosomal recessive, and sporadic ataxias. Most of the degenerative ataxias are hereditary disorders. A diagnosis of degenerative ataxia often starts with the exclusion of other causes of cerebellar ataxia (vascular disease, inflammatory disorders, neoplasia, toxic causes, metabolic causes). Degenerative ataxias from typically have a slow progressive rate over many years. The onset of slowly progressive ataxia in childhood implies very probably recessive degenerative ataxia; the onset in adult age dominant ataxia, the onset of sporadic disorders tends to be late in life.

Main clinical features are gait ataxia, dysarthria and oculomotor abnormalities; later upper limb ataxia, clumsiness and writing problems. The cerebellum is prominently affected, but other systems are affected as well (pyramidal tract involvement, sensory impairment, axonal neuropathy, extrapyramidal signs, spinal tract pathology). Some other signs can rarely draw the clinical picture; retinal impairment, orthostatic hypotension, epileptic seizures, cognitive decline. Also, non-neurological abnormalities such as scoliosis, cardiomyopathy, cataract, skin abnormalities etc. may accompany the neurological signs. MRI shows pronounced cerebellar atrophy, with the involvement of another brain regions; based on the SCA type, severity, and duration of the illness.

Various scales were introduced to assess the severity of ataxia: the International Cooperative Ataxia Rating Scale (ICARS) or the Scale for the Assessment and Rating of Ataxia (SARA).

There is no therapy to prevent neuronal cell death in ataxia or even delay the age of onset. However, defining the genetic causes of the SCA subtypes might give some directions for the treatment of certain symptoms. Currently the therapy is only symptomatic.

#### 4. Transdermal delivery of rotigotine in the treatment of Parkinson's disease

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The concept of Continuous Dopaminergic Stimulation (CDS) is one of the main keys to prevent the motor complications in Parkinson's disease (PD). Recent advances in the field of neuropharmacology allowed to introduce transdermal delivery of new dopamine agonist, rotigotine which offers to achieve better control of parkinsonian symptoms in early PD as well as advanced PD. Rotigotine is a non-ergolinic dopamine agonist and can be applied once daily. The advantages of rotigotine include ease of use, constant drug delivery and avoidance of gastrointestinal absorption. The patients' compliance could be improved, too. The disadvantages of the rotigotine patch are skin irritation, smaller adherence, and crystallization of the drug which needs to be kept in the refrigerator. Recently published data showed that continuous delivery of rotigotine via the transdermal system enabled better control of non-motor symptoms like sleep problems, fatigue, mood, cognition, and pain. Quality of life aspects were improved as measured by short-form Parkinson's Disease Questionnaire (PDQ-8). Adverse event profile is similar to other dopamine agonists. Transdermally delivered rotigotine is a clinically innovative and useful addition to the class of the dopamine agonists.

#### 5. Changes of Basal Ganglia Detected by Transcranial Sonography and 123I FP-CIT SPECT

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**Purpose:** Diagnosis of Parkinson's disease (PD) could be difficult in early stages of the disease. Transcranial sonography (TCS) is able to detect structural changes in substantia nigra in PD patients. FP-CIT SPECT imaging could detect presynaptic dysfunction in several neurodegenerative diseases. The aim of our study was to assess correlation between TCS and SPECT findings and diagnosis of PD, other parkinsonian syndromes (PS), essential tremor (ET) and psychogenic movement disorder (PMD).

**Methods:** We examined 25 patients (19 male, mean age 57.2 ± 8.4 years) during two years – four patients with ET, 12 PD patients, seven PS patients, and two PMD patients. SN echogenicity and SN area were detected using TCS and SPECT evaluation of basal ganglia were performed using SPECT with DAT-ligand (123I-ioflupan) within two months after clinical examination. The sensitivity, specificity, positive predictive (PPV) and negative predictive (NPV) values for TCS and SPECT were evaluated.

**Results:** TCS/SPECT sensitivity, specificity, PPV and NPV for diagnosis of PD or PS were 77.8%/72.2%; 57.1%/100%; 82.4%/100% and 50.0%/58.3%. TCS and SPECT findings correlated in 68% of patients.

**Conclusion:** TCS has higher sensitivity but significantly lower specificity for detection pathologies in PD/PS patients in comparison with SPECT.

#### 6. Progressive Supranuclear Palsy

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Progressive supranuclear palsy (PSP, Steele-Richardson-Olszewski disease) is a progressive neurodegenerative disorder, which presents with supranuclear gaze palsy, bradykinesia, axial rigidity, early postural instability with falls, and frontolimbic dementia. It has been described for the first time in 1963 (despite several reports may have picked up this disease since the late 19<sup>th</sup> century), but only in the following decades PSP has been characterized more in detail from the biological, pathological and clinical point of view. In two recent epidemiological studies in the UK, the age-adjusted prevalence of PSP was 5.4–6.0/100,000. In these studies, the median age of onset was 65–69 years, and the median disease duration at death was 4–5.5 years. No clear risk factors have been identified until now in the few case-control studies available. Over the last decade, a wide heterogeneity of the disease into different clinical subtypes (classic variant or Richardson syndrome, pure parkinsonian variant, corticobasal syndrome, pure akinesia, focal cortical syndromes) has been recognized. This is the reason of the poor sensitivity of the currently available diagnostic criteria for PSP, which are mainly designed to detect cases of classical PSP. Neuroimaging

features and CSF studies may support the diagnosis, but true biomarkers are still lacking in the clinical setting. Neuronal and glial tau positive aggregates are predominantly found in basal ganglia brainstem and primary motor cortex, and tau-positive astrocytic tufts help to confirm the diagnosis. In variants of PSP presenting with focal cortical syndromes, such as frontotemporal dementia, corticobasal syndrome and apraxia of speech, there is greater cortical pathology than in typical PSP. Conversely, in variants of PSP presenting with levodopa-responsive parkinsonism, as well as pure akinesia and gait freezing, there is less cortical pathology and more severe degeneration of the globus pallidus, subthalamic nucleus and substantia nigra than in typical PSP. A significant association of PSP with the common H1 tau haplotype likely points to a pathophysiological role of the tau protein in the disease process. Genetic studies of familial cases and an ongoing genome-wide association study of large series of pathologically-proven cases may hopefully reveal additional genetic factors. Despite the disappointing results from the first trials with Coenzyme Q10 and riluzole, several international groups are conducting multicentre intervention trials with possible disease-modifying agents in PSP. These trials could change our approach to this disease, also providing previously unavailable prospective data concerning disease progression that can be used to identify reliable predictors of survival.

## 7. Dyskinesia as a Result of Toxic Brain Damage – a Case Report

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Our patient – a 58-year-old woman – has a history of cholecystectomy in 1997, a gynecological surgery in 2007 (without irradiation) and she suffered from transient brain ischemia one year ago.

16th June 2010: she was admitted somnolent to the ward of internal medicine. The somnolence deteriorated in two days to coma, lung ventilation was introduced after intubation. The CT scan found out developing ischemias of bilateral thalamus with a suspicion of thrombosis of deep brain veins. The patient was transferred to our clinic to the intensive care. At this timepoint there was a tonic deviation of eyes upwards and quadraparesis with only limited flexion after painful stimulation and bilateral Babinski sign. Tracheostomy was done. There was elevated CRP (243), leukocytes (20.9) with majority of segments in laboratory. MRI revealed small ischaemic lacunes in both thalamus, in the area of posteromedial branches of PCA, after contrast medium the failure of blood brain barrier was clear. MR angiography (arterial and venous phase) was normal. Lumbar puncture was done – protein 0.28 g/l; Cl 124; lactate 1930; K 4.4. Cytology of CSF was normal. After four days a very slow regression of unconsciousness started and the quadraparesis improved as well. Dyskinesias of tongue appeared with protrusion, pouting of perioral muscles. There were no palatal and cervical movements.

Antibiotic treatment was given because of suspicion of staphylococcal infection. But the clinical course was unusual (unconsciousness from somnolence to coma and then regression) we searched for possible intoxication or other reason. The relatives told us eventually, that the patient cleaned the bathroom with a special cleaning agent and after that she was weak and somnolent, which was the reason for admission to the hospital.

We suppose this case was an intoxication with unconsciousness and toxic brain damage, which caused the damage of corticospinal tracts, deviation of eyes and the failure of blood brain barrier. Intoxication and perhaps following metabolic and vascular changes were reasons of the development of dyskinesias of tongue and lips.

## 8. “PSP-like” Parkinson’s Disease, or Can we Really Reliably Diagnose Using Clinical and Paraclinical Methods?

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Diagnostic criteria for Parkinson’s disease (PD, Hughes 2002) and progressive supranuclear palsy (PSP, Litvan 1996) are considered as a relatively useful tool for clinical differentiation of both neurodegenerative diseases. However, not any criteria supposed possibility of such manifestation of Parkinson’s disease, which would copy the clinical phenotype of PSP: markedly rigid and bradykinetic parkinsonian syndrome without tremor, mixed dementia with dominant subcortical component, gait apraxia and supranuclear gaze palsy including eyelids opening apraxia.

Our patient manifested first parkinsonian signs at the age of 53 years. During the next three years, the L-dopa responsive parkinsonian syndrome with typical dementia, upward gaze palsy, eyelid apraxia, gait apraxia and without tremor developed. Sudden falls and typical Lhermitt’s frontal signs appeared several months later, the response to L-dopa disappeared consequently. Clinical signs and the lab findings (MRI, electrophysiology) suggested the diagnosis of PSP. After the next three years

the patient died due to the cardiac disease. The pathologic and histopathologic examination of patient's brain and evaluation of its results by two independent pathologists confirmed only the changes typical for Parkinson's disease. This case surely implies question about overlap of phenotypes of different neurodegenerative diseases with parkinsonian syndrome as a dominant in the clinical picture.

## 9. Paraneoplastic Chorea Associated with Breast Cancer

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Paraneoplastic neurological syndromes are remote immunological complications of cancer. They are not caused by tumor invasion or metastasis, infection, ischemia, or tumor treatment. Their diagnosis is difficult, because clinical markers are often absent and symptoms usually precede the diagnosis of cancer. However, diagnosis can be facilitated by finding immunoreactive changes in the cerebrospinal fluid and blood, mainly antineuronal antibodies that are associated with specific clinical syndromes and tumor types.

We report on a 60-year-old woman who developed acute psychosis and chorea two months before the diagnosis of breast cancer. The laboratory work-up was positive for the antineuronal autoantibodies (anti-Hu and anti-Ri). Pulsed therapy with methylprednisolone did not result in any clinical improvement of chorea. The patient appears to be a unique case of chorea resulting from paraneoplastic encephalopathy associated with breast cancer.

## 10. FTLD-TDP with Motor Neuron Disease and Progressive Supranuclear Palsy-like Syndrome – a Distinct Phenotype?

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Frontotemporal lobar degeneration with ubiquitin and TDP-43 positive neuronal inclusions represent a novel entity (FTLD-TDP) that may be associated with motor neuron disease (FTLD-MND); involvement of extrapyramidal and other systems has also been reported.

We present three cases with similar clinical symptoms, including parkinsonism, supranuclear gaze palsy, and a behavioral variant of frontotemporal dementia, associated with either clinically possible or definite MND. Neuropathological examination revealed hallmarks of FTLD-TDP with major involvement of subcortical and, in particular, mesencephalic structures.

These cases differed in onset and progression of clinical manifestations as well as distribution of histopathological changes in the brain and spinal cord. Two cases were sporadic, whereas the third case had a pathological variation in the progranulin gene 102delC.

Association of a "progressive supranuclear palsy-like" syndrome to motor neuron disease and early behavioral disturbances may represent a clinically distinct phenotype of FTLD-TDP. Our observations further support the concept that TDP-43 proteinopathies represent a spectrum of disorders, where preferential localization of pathogenetic inclusions and neuronal cell loss defines clinical phenotypes ranging from frontotemporal dementia with or without motor neuron disease, to corticobasal syndrome to a progressive supranuclear palsy-like syndrome.

## 11. Corticobasal Degeneration

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Corticobasal degeneration (CBD) is a neurodegenerative disorder of unknown cause. It was first described in the late 1960's. Patients present with dysfunction of the cerebral cortex (thus the term "cortico-") and the basal ganglia (thus the term "basal"). Signs are usually strikingly asymmetric. Cortical signs manifest as poor coordination and apraxia of the limbs, which



in the late stages of the disease act “as if having a mind of their own” (alien limb phenomenon), cortical sensory loss, aphasia, amnesia and myoclonus. Basal ganglia signs manifest as bradykinesia, rigidity, dystonia, and tremor. Some patients develop personality and behavioral changes.

Pathophysiologically, CBD is a proteinopathy, a tauopathy. It is estimated to account for about 5% of cases of parkinsonism seen in clinics that specialize in movement disorders, or 0.62–0.92 per 100,000 per year, with an estimated prevalence of 4.9–7.3 per 100,000. The average age for the onset of symptoms is 67 years. No pathologically confirmed case of CBGD has ever been published with onset before 45 years. The rate at which symptoms progress can vary widely between individuals, but people typically live for around eight years after the onset of symptoms.

**Treatment:** anticholinergics and other medications that impair attention and memory and medications that may cause parkinsonism should be stopped. Vitamin E and SSRI should be considered along with levodopa/carbidopa and botulinum toxin injections for painful limb dystonia. As the disease advances, the whole multidisciplinary team should be included: occupational, physical, and speech therapists, as well as psychologist, dietitian and social worker.

## 12. Idiopathic REM Sleep Behaviour Disorder – State at Diagnosis and Four Years Later

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REM sleep behaviour disorder (RBD) is characterized by loss of muscle atonia during REM sleep and by dream content enactment. There are two RBD forms: idiopathic RBD (iRBD) and RBD associated with other diseases such as narcolepsy or alpha-synucleinopathies.

We diagnosed 16 patients (13 men and 3 women) with iRBD over a period of 9.5 years. Their average age was 66.4 years (46–77).

The iRBD patients' history was free from any neurodegenerative disease or sleep disorder. 94% of them were referred to us for RBD symptoms. 38% complained of excessive daytime sleepiness, 25% of the restless legs syndrome. Their neurological condition was within norm, their BMI – 27.1 ( $\pm$ 4.1).

Night polysomnography showed typical muscle tone disturbance in REM sleep, considerable sleep fragmentation and low sleep efficiency (69.8  $\pm$ 17.8%). The sleep apnoea syndrome was diagnosed in 81%, the periodic limb movement syndrome in 63% of the cases.

Twelve patients were re-examined after 3.7 years. None reported any worsening of RBD symptoms; ten patients treated with clonazepam declared its positive effect.

Three male patients developed neurological involvement: mild cognitive deficit after seven years, suspected Lewy body disease after four years and multiple system atrophy after one year from the RBD diagnosis.

The results are in accordance with studies describing the fact that iRBD precedes the development of diseases with parkinsonian syndrome and dementia.

## 13. The Profile of CSF Neurodegenerative Markers in Different Phenotypes of Parkinson's Disease

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**Background and Objective:** The clinical manifestation of Parkinson's disease (PD) is very heterogeneous, which inspired many attempts to divide PD patients into clinical subgroups. This could lead to a better recognition of pathogenesis, improving targeted treatment and prognosis in PD patients. The aim of the present study was to obtain CSF samples in PD patients and to search for a relationship between neurodegenerative CSF markers (tau protein, beta-amyloid1-42 and index tau/beta) and the clinical subtypes.

**Methods:** PD patients were divided into three subgroups – early disease onset (EDO), tremor-dominant PD (TD) a non-tremor dominant PD (NT) according to previously published classification. Neurodegenerative markers in the CSF were assessed in these three groups of patients suffering from PD (EDO-17, TD-15, NT-16 patients) and in a control group (CG) of 19 patients suffering from non-degenerative neurological diseases.

**Results:** The NT-PD patients were found to have significantly higher levels of CSF tau protein and index tau/beta than the control subjects and also than other parkinsonian subgroups.

**Conclusion:** Significantly higher tau protein and index tau/beta CSF levels in the group of NT-PD patients probably reflect incipient pathology associated with cognitive impairment, even though the patients were without cognitive deficit at this stage.

## 14. Dementia with Lewy Bodies

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Dementia with Lewy bodies (DLB) is clinically characterized by progressive dementia, fluctuating cognition, variations in attention and alertness, recurrent visual hallucinations and spontaneous parkinsonian motor symptoms. REM sleep behavior disorder, neuroleptic hypersensitivity, and early urinary incontinence are suggestive of DLB. Dementia occurs not later than one year after the onset of parkinsonian motor features. In a small minority parkinsonian motor symptoms develop months to years after the onset of dementia and hallucinosis. There is overlap and similarity to dementia in Parkinson's disease. The underlying pathology is Lewy bodies, Lewy neurites, neuronal loss and Alzheimer-type lesions (in the majority of patients). CT or MRI reveal diffuse or fronto-temporo-parietal cortical atrophy with relative preservation of the hippocampus. Dopamine (Fluorodopa PET) and dopamine transporter imaging (FP-Cit,  $\beta$ -Cit SPECT) show reduced striatal signals. EEG is often abnormal (diffuse slowing). Neuropsychological testing reveals impairment of visuospatial functions, memory, word list generation, frontal-dysexecutive and attentional deficits and a slowing of cognition. Patients respond to a lesser degree to levodopa than in PD without dementia. Rivastigmine is effective in improving cognition and also behavioral symptoms. Small studies have shown, at a lower level of evidence, that donepezil, reminyl and memantine might be effective. The best possible agent to treat psychosis is clozapine, together with a reduction of dopaminergic substances. Anticholinergics, such as trospium Cl, improve urinary incontinence, however, central and peripheral anticholinergic side effects may occur. Orthostatic hypotension is treated with fluid intake, fluorocortisone and midodrine. Patients with DLB tend to fall and injuries are frequent complications. The disorder often progresses more rapidly than Alzheimer's disease (AD). Differential diagnoses are AD, mixed and vascular dementia, steroid-sensitive encephalopathy, frontotemporal lobar degeneration including PSP and CBD, and, in rare cases, also prion diseases, such as CJD.

## 15. Pathology of Atypical Parkinsonian Syndromes

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The term atypical parkinsonian syndromes describes a pathologically heterogeneous group of neurodegenerative disorders clinically characterized by parkinsonism, in addition to signs atypical for Parkinson's disease such as pyramidal tract signs, myoclonus, supranuclear gaze palsy, apraxia, cerebellar ataxia, early autonomic dysfunction or early dementia. The group of atypical parkinsonism includes diverse disease entities such as progressive supranuclear palsy (PSP), corticobasal degeneration (CBD), multiple system atrophy (MSA) and dementia with Lewy bodies (DLB).

PSP and CBD are sporadic, "primary" tauopathies and both diseases are characterised pathologically by neuronal and glial inclusions composed of abnormal, hyperphosphorylated (4-repeat) tau. Evidence also suggests a similar genetic link between the tau gene (H1 haplotype) and development of both disorders. Despite the similarities, there are robust neuropathological differences in the tau pathology between the two conditions (for example tufted astrocytes in PSP and astrocytic plaques in CBD), which allow a specific morphological diagnosis to be made. Clinicopathological studies have also demonstrated different subtypes of PSP with characteristic clinical presentation, tau biochemistry and neuropathological findings (Richardson's syndrome, PSP-Parkinsonism and pure akinesia with gait freezing). Other subdivisions of PSP are primarily based on differences in the severity and distribution of the tau pathology.

MSA is a primary degenerative disease of the nervous system that is neuropathologically defined by the presence of cellular inclusions occurring predominantly in oligodendrocytes (glial cytoplasmic inclusions or GCIs). Although patients with parkinsonism (MSA-P) may show a preponderance of pathology in the striatonigral system while patients with predominant cerebellar signs (MSA-C) may have the principal pathology in the olivopontocerebellar system with variable striatonigral degeneration, an equal involvement of the striatonigral and olivopontocerebellar systems is the most common neuropathological variant. In all varieties of MSA there is usually involvement of the autonomic nervous system. Microscopically glial and neuronal cytoplas-

mic and nuclear inclusions occur extensively in MSA. The primary protein component of all types of inclusion, including GCIs is  $\alpha$ -synuclein; hence MSA is defined as one of the synucleinopathies.

The term DLB is used to describe a characteristic clinical syndrome with dementia, hallucinations, fluctuation in the level consciousness and parkinsonism. As in end stage Parkinson's disease with dementia (PDD), the neuropathology in most DLB cases is that of widespread cortical, subcortical and brainstem Lewy bodies, which are also composed of aggregated  $\alpha$ -synuclein protein. A significant proportion of the cases also have some degree of Alzheimer-type pathology (amyloid plaques and neurofibrillary tangles). The implication of this is that an important interaction between Lewy- and Alzheimer-type pathologies has emerged in recent experimental and neuropathological studies in both DLB and PDD, emphasizing the significance of both types of pathologies in the progression of Lewy body disorders.

## 16. DYT3, X-linked Dystonia Parkinsonism – Then and Now

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From its first recognition as a unique phenomenology and being indigenous in the Philippines, X-linked Dystonia Parkinsonism (XDP, also known as "Lubag") has come to be known through the print publication by Lee and cohorts in 1976. The clinical phenotype of XDP is typically one that involves a Filipino adult male whose ancestry is mostly traced in the Philippine island of Panay. Dystonia usually starts focally in the lower limbs or oromandibular regions, then spreads to become generalized eventually. Parkinsonism sets in later into the disease and usually in combination with dystonia. The cranial MRI shows hyperintense putaminal rim in both dystonic and parkinsonian stages, and atrophy of the caudate head or putamen in the parkinsonian stage. Neuropathological findings show atrophy of the caudate nucleus and putamen, with mild to severe neuronal loss and gliosis. In the neostriatum, the dystonic phase of XDP shows involvement of striosomes and matrix sparing, while the later, parkinsonian phase shows matrix involvement as well. In the dystonic phase, the loss of striosomal inhibitory projections lead to disinhibition of nigral dopaminergic neurons perhaps resulting in a hyperkinetic state; while in the parkinsonian phase, severe and critical reduction of matrix-based projection may result in extranigral parkinsonism. Now, and with the advent of genetic study collaborations (DYT3) and (TAF1) have become known as the two genes associated with XDP. An SVA retrotransposon insertion in an intron of (TAF1) may reduce neuron-specific expression of the (TAF1) isoform in the caudate nucleus, and subsequently interfere with the transcription of many neuronal genes. Interestingly, occurrence of affected female cases in kindreds with XDP, is opening an avenue for a better understanding of disease penetrance. Polypharmacy with oral benzodiazepines, anticholinergic agents and muscle relaxants leaves much to be desired in terms of efficacy. The medications to date that may appear beneficial, especially in disabling dystonias, are zolpidem, muscle afferent block with lidocaine-ethanol and botulinum toxin type A. Despite the few cases undergoing deep brain stimulation, this functional surgery has shown the greatest promise in XDP. There remain some gaps in understanding some phenomenological, genetic and treatment aspects of XDP, the areas upon which future research directions may be worthwhile.

## 17. Atypical Parkinsonian Syndromes – Where are we Now?

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Parkinsonian syndrome (PS) is defined as a combination of at least two following symptoms: akinesia, rigidity, rest tremor, postural and gait disorder. In general, PS is caused by the dopaminergic (DAergic) deficit in the striatum, caused by the loss of DAergic cells in the substantia nigra. Only very rarely, PS or symptoms mimicking PS are caused by lesions in other brain regions (striatal lesion without the nigral loss, frontal white matter lesions etc.).

Parkinson's disease (PD) is the most common cause of PS. However, approx. 20–30% of all patients manifesting PS have secondary, symptomatic PS, including the heterogenous group of neurodegenerative diseases, covered by the term atypical parkinsonian syndromes (APS) or formerly parkinson + syndromes.

According to the histopathology findings of various protein accumulation, APS are classified into two subgroups:  $\alpha$ -synucleinopathies (multiple system atrophy, dementia with Lewy bodies, neurodegeneration with brain iron accumulation, and also PD) and tauopathies (progressive supranuclear palsy, corticobasal ganglionic degeneration, frontotemporal dementia with parkinsonism linked to chromosome 17, amyotrophic lateral sclerosis and parkinsonism-dementia complex or Lytico-Bodig).



Atypical nature of APS could be characterized by a rapid progression, a poor response to DAergic stimulation and a presence of symptoms, that are atypical in PD (eg. pyramidal, cerebellar signs, supranuclear gaze palsy), or at least atypical in the early stages of PD (eg. dementia, postural instability with falls, dysautonomia). APS also have different (although so far unknown) etiology, pathophysiology, histochemistry and neuropathology.

However, before the initiation of the DAergic therapy, PD had the same prognosis and time course as APS nowadays. Moreover, in the clinical picture of the advanced stages of PD, the most debilitating symptoms are hallucinations, incontinence, psychosis, dementia, falls etc. These are, in fact, symptoms characteristic for APS.

Where are we now with our understanding to APS?

1. in the period of the crisis in our nosological classification of diseases.
2. in the period, where the enormous increase of knowledge in both basic and clinical science does not lead to any real breakthrough for our APS patients.

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## 18. Differential Diagnosis of Atypical Parkinsonian Syndromes

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Atypical parkinsonian syndromes (APS) comprise numerous disorders characterized by variable combinations of hypokinesia, rigidity, tremor and postural abnormalities. In general, APS are induced by lesions or functional involvement of the basal ganglia and their connections. In contrast to Parkinson's disease (PD), the nigrostriatal dopaminergic pathway is not primarily involved and dopaminergic therapy is usually ineffective. APS can be classified according to their causes in the categories of neurodegenerative diseases other than PD and secondary (symptomatic) parkinsonian syndromes.

The differential diagnosis of APS is based on the presence of a) parkinsonian syndrome; b) additional symptoms and signs (Table 1); c) dopaminergic nonresponsiveness and d) typical laboratory and/or imaging findings.

In neurodegenerative APS, progressive supranuclear palsy (PSP, morbus Steele-Richardson-Olszewski) and multisystem atrophy (MSA) represent the most frequent entities, with the prevalence of up to 5/100,000, while corticobasal ganglionic degeneration (CBGD) is a rarer disease. In this category, also dementia with Lewy bodies (DLB) and subtypes of spinocerebellar ataxias (SCA) can be listed.

Secondary APS include postencephalitic parkinsonism, antidopaminergic drug-induced parkinsonian syndrome, toxic and metabolic syndromes due to deposition of copper, manganese or calcium in the basal ganglia. Vascular parkinsonism or normal pressure hydrocephalus (NPH) are often misdiagnosed as PD or APS despite a rather specific disorder of gait that is accompanied with typical brain imaging.

Finally, psychogenic parkinsonism should be correctly recognized and appropriately managed to avoid excessive diagnostic and treatment procedures.

**Table 1. Additional symptoms and signs.**

Additional symptoms or signs	Possible diagnosis
early instability and falls	PSP, vascular encephalopathy, NPH
oculomotor disorder	PSP
early dementia	DLB, PSP, vascular encephalopathy
dystonia	MSA, Wilson's disease
dysautonomia	MSA
cerebellar ataxia	MSA, SCA, Wilson's disease

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## 19. Postneuroleptic Parkinsonian Syndromes

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Neuroleptic-induced parkinsonism (NIP) became apparent only a few years after the introduction of chlorpromazine in the early 1950's. In fact, it was recognized that the clinical features of parkinsonism induced by neuroleptics were virtually indistinguishable from idiopathic Parkinson's disease (IPD) long before the relationship between dopamine deficiency and parkinsonian symptomatology became apparent. Nowadays it is widely accepted that D2-receptor blocking causes NIP. Although NIP may mimic all the features encountered in IPD, the most common and earliest clinical feature is akinesia, while rigidity and especially the cogwheel phenomenon or tremor, respectively, are rarer. In contrast to IPD, however, NIP can be symmetrical and may go along with "rabbit syndrome", akathisia, or other tardive features which therefore may be useful for differential diagnosis. NIP is usually dose dependent for each drug and related to dopamine D2 striatal receptor occupancy induced by the antipsychotic drug, but does not correlate with their antipsychotic activity. Newer "atypical" antipsychotics may have a lower potency to induce NIP. Usually, NIP wanes slowly over weeks after withdrawal of the offending drug, however, in 15% of patients with a history of antipsychotic therapy NIP never does resolve. Established risk factors for developing NIP are female gender, advanced age, and basal ganglia abnormalities as seen on MRI, yet the susceptibility of certain individuals to NIP still remains a matter of debate: especially those 15% of patients whose NIP does not improve within several weeks may probably be individuals with presymptomatic IPD; as post-mortem data is contradictory this issue needs further investigation. Treatment can be challenging: while withdrawal is most suitable option and dopaminergic substitution may be tried in those that do not recover spontaneously, in most psychiatric patients this is not viable and a switch to atypical antipsychotics and especially clozapine can be tried. Unlike in acute neuroleptic-induced movement disorders, anticholinergics usually are of limited use.

## 20. Sleep Disorders in Parkinson's Disease and their Management

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Although James Parkinson mentioned sleep disturbances in Parkinson's disease (PD) as early as 1817 and although PD is associated with all types of sleep abnormalities, only scarce attention has been paid to this particular symptom until recently. Only the past two decades have shown sleep disorders in PD as frequent comorbidities likely to complicate the patients' lives very much. According to our questionnaire study, 32% of them have problems getting off to sleep, 42% take long to resume sleep after nocturnal arousal, 44% suffer from daytime sleepiness and 49% report evening and nocturnal restlessness of limbs. Also worth noting is the frequent incidence of insufficient muscle atonia in REM sleep and its behavioral manifestations (REM behavior disorder, RBD). Poor-quality nocturnal sleep requires treatment for comorbidities (apnea, periodic limb movement in sleep, depression etc), dopaminergic therapy optimization (a longer half-time is an advantage there) and/or sodium oxybate and hypnotics. Treatment for excessive daytime sleepiness means, primarily, better nocturnal sleep quality, if possible, and initiation of optimum PD therapy. Modafinil and sodium oxybate can be used. Symptomatic treatment for RBD makes use of evening doses of clonazepam.

## 21. Multiple System Atrophy – from Bench to Bedside

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Multiple system atrophy (MSA) is an atypical parkinsonian disorder clinically characterized by dysautonomia, parkinsonism, cerebellar symptoms, and pyramidal signs in any combination. Histopathological hallmark features include – synuclein positive glial cytoplasmic inclusions (GCIs) that are associated with a distinctive neuronal multisystem degeneration involving striatonigral, olivopontocerebellar and central autonomic pathways. Due to loss of striatal projection neurons parkinsonism in MSA is usually unresponsive to dopaminergic therapy. Disease is rapidly progressive and life expectancy markedly reduced with a median survival of 7–9 years. Failure of symptomatic treatment raises an urgent need for disease modifying strategies.

Over the last decade both toxin-induced and transgenic MSA animal models have become available to screen candidate agents (Stefanova 2005). Neuroprotective effects have been reported for riluzole (Scherfler 2005), minocycline (Stefanova 2007), rasagiline (Stefanova 2008) and rifampicine (Ubhi 2008). In contrast, disease modification trials of minocycline (Dodel et al 2010) and riluzole (Bensimon 2009) have been negative highlighting the need for optimization not only of trial protocols but also of preclinical study designs including selection of animal models and appropriate interventions.