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New insights into atypical parkinsonism

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Abstract

Purpose of review—Atypical parkinsonian disorders (APDs) comprise a heterogenous group of disorders including multiple system atrophy (MSA), dementia with lewy bodies (DLB), progressive supranuclear palsy (PSP) and corticobasal degeneration (CBD). Based on literature published in 2010 we here review recent advances in the APD field.

Recent findings—Genome-wide association studies have provided robust evidence of increased disease risk conferred by synuclein and tau gene variants in MSA and PSP. Furthermore, advanced imaging tools have been established in the differential diagnosis and as surrogate markers of disease activity in APD patients. Finally, although therapeutic options are still disappointing, translational research into disease-modifying strategies has accelerated with the increasing availability of transgenic animal models, particularly for MSA.

Summary—Remarkable progress has been achieved in the field of APDs and advances in the genetics, molecular biology and neuroimaging of these disorders will continue to facilitate intensified clinical trial activity.

Keywords

Multiple system atrophy; Progressive nuclear palsy; Corticobasal degeneration; Dementia with Lewy bodies

Introduction

Movement disorders experts are increasingly challenged by atypical parkinsonian disorders (APDs) that include α -synucleinopathies (multiple system atrophy (MSA), dementia with Lewy bodies (DLB)) and tauopathies (progressive supranuclear palsy (PSP), and corticobasal degeneration (CBD)). APDs are characterized by relentlessly progressive and levodopa refractory parkinsonism associated with a range of distinctive atypical features [1**]. We here review recent developments in APD research covering preclinical as well as clinical aspects.

Synucleinopathies

α -synuclein is the main component of the inclusion pathology in MSA and DLB classifying these two disorders among other α -synucleinopathies such as PD and pure autonomic failure.

Multiple System Atrophy

While there has been relatively little progress in the clinicopathological understanding of MSA a number of transgenic models have recently generated important insights into glial synuclein-associated neurodegeneration that have stimulated interventional neuroprotection trials in MSA patients [2].

Molecular pathogenesis—The working hypothesis of MSA as a primary oligodendroglial pathology with prominent (oligodendro-) glial cytoplasmic inclusions and secondary neuronal multisystem degeneration [3] has recently been corroborated by the discovery of deficient oligodendroglial GDNF release associated with selective neuronal loss in a transgenic MSA mouse model [4]. Extending previous findings (Song 2007) tubulin polymerization promoting protein (TPPP) also known as p25 α was shown to specifically accelerate oligodendroglial α -synuclein oligomer formation and to promote α -synuclein-positive GCI-like inclusions [5]. The concept of protein seeding and disease propagation has received increasing attention due to the discovery of Lewy body formation in embryonic grafts of patients with Parkinson's disease (PD) [6]. Similar mechanisms may also play a role in MSA although there are no convincing experimental or postmortem data [7]. Of note, cerebrospinal fluid (CSF) from patients with MSA seems capable of promoting in vitro α -synuclein fibril formation [8].

Genetics—Several independent research groups identified an association of single nucleotide polymorphisms (SNP) within the α -synuclein gene locus (SNCA) and increased MSA disease risk [9*, 10, 11]. However, these findings were not replicated in a Korean study due to high SNP frequencies in the control population [12]. Although a number of MSA pedigrees have been reported consistent with mendelian disease no genes have been identified to date [13, 14].

Clinical studies—The clinical presentation of MSA has been characterized in greater detail by a prospective EMSA study analyzing 437 MSA patients in 19 different European study sites [15**]. In accordance with previous studies, patients with MSA exhibited early and severe autonomic involvement with urinary disturbances, postural instability due to orthostatic hypotension and gastrointestinal symptoms [15**, 16]. Surprisingly, only one-third of patients with either documented orthostatic dysfunction or bladder disturbances received appropriate treatment [15**]. This finding emphasizes the urgent need for additional guidelines in this area. Dementia is regarded an exclusion criterion according to the consensus diagnostic criteria for MSA [17]. In contrast, data from a large prospective study assessing the natural history of MSA suggest that significant cognitive impairment develops in a substantial proportion of patients with MSA, often early in the disease [18]. Sleep disturbances may occur in up to 70% of MSA patients with rapid eye movement

(REM) sleep behavior disorder (RBD) being the most common presentation [16]. Insomnia and excessive daytime sleepiness (EDS) occur less frequently (19% and 17%, respectively) [15**]. Additionally, up to 30% of patients have symptoms consistent with a restless legs syndrome [15**, 19*]. Interestingly, RBD may not only be a concomitant feature in the disease course but may also precede other clinical aspects by several years [20]. An intriguing polysomnographic study in levodopa-refractory MSA patients demonstrated improved facial expression, improved speech and limb movements during RBD [21], suggesting compensatory involvement of cerebellar and other non-basal ganglia motor circuits [21].

Depression, anxiety and pain are disabling symptoms of MSA. In a recent series 43% of MSA patients had probable depression according to the “Hospital Anxiety and Depression Scale” (HADS) [22]. In addition, this series revealed that more than 50% of patients with MSA suffer from anxiety [22].

Diagnostic work-up—The relevance of additional investigations in early suspected MSA remains unclear, however, neuroimaging appears to contribute most to diagnostic accuracy.

The predictive value of baseline putaminal abnormalities on 3-T MRI in differentiating early MSA-P from PD was assessed in a 3-year follow-up study [23]. A sum score based on putaminal abnormalities was highly specific (93%) at the expense of sensitivity (70.6%) [23]. In a voxel-based morphometry MRI approach, annual tissue-loss profiles revealed white matter reduction within the middle cerebellar peduncles in MSA patients consistent with degeneration of the ponto-cerebellar tract [24]. Additionally, white matter reduction along the corpus callosum at follow-up was reported suggesting a possible disease-specific pattern of neurodegeneration and cortical atrophy [24]. Diffusion tensor imaging (DTI) showed microstructural white matter abnormalities in patients with MSA-C suggesting that DTI may serve as a useful surrogate marker [25].

In a large cohort of patients with parkinsonian disorders a recent study showed high positive predictive values of automated metabolic expression patterns using fluorine-18-labelled-fluorodeoxyglucose positron emission tomography (FDG-PET). MSA patients were classified with a sensitivity of 85% and a specificity of 96% reflecting a 97% positive predictive value (PPV) and an 83% negative predictive value (NPV) [26*]. Similarly, a computer-assisted approach following an automated observer-independent algorithm was superior to a rater-based approach in classifying a sup¹²³I-β-CIT-SPECT image to either PD, MSA, PSP and healthy age-matched controls [27]. These findings suggest that automated image-based classification may help in discriminating MSA, PSP and PD in early-stage patients. As mentioned previously RBD may precede neurodegenerative disorders associated with loss of nigral dopaminergic neurons. In these patients, ¹²³I-2β-carbomethoxy-3β-(4-iodophenyl)-N-(3-fluoropropyl)-nortropane (¹²³I-FP-CIT) SPECT and transcranial sonography (TCS) were able to detect subclinical changes (i.e. decreased striatal ¹²³I-FP-CIT binding and substantia nigra hyperechogenicity) which might be useful markers to identify individuals at increased risk for development of PD, DLB or MSA [28]. A PET study assessing motor activation in MSA compared to PD showed activated cerebellar pathways in PD patients whereas MSA patients recruited frontoparietal cortical areas, likely

reflecting compensation of basal-ganglia and cerebellar dysfunction [29]. ¹²³I-Meta-iodobenzylguanidine (MIBG) myocardial scintigraphy has been proposed as a useful tool to separate MSA from PD [30]. However, a recent longitudinal study showed decreased cardiac MIBG uptake in up to 30% of MSA patients irrespective of disease duration or severity [31]. Concurrent sympathetic Lewy body pathology may rarely accelerate cardiac denervation in such MSA patients [32]. Widespread brainstem, white matter and cortical α -synuclein deposition correlating with GCI density at postmortem was reported in 8 MSA patients using PET and ¹¹C-2-[2-(2-dimethylaminothiazol-5-yl)ethenyl]-6-[2-(fluoro)ethoxy]benzoxazole [33*], suggesting that in-vivo synuclein PET imaging may represent a novel surrogate marker of MSA.

The work-up of autonomic failure in MSA is mostly based on cardiac autonomic, neuroulogical and sudomotor tests. In a prospective study assessing the discriminative value of multiple cardiac autonomic and sudomotor indices demonstrated that MSA and PD may be separated by the severity, distribution, and pattern of autonomic deficits – even at study entry [34]. Multiple sensor pressure transducer measurements of bladder and urethral pressure characterized detrusorurethral dyssynergia in MSA patients more accurately than a single global measurement in a recent prospective study. Detrusor-underactivity was noted in 58% of MSA patients within 4 years of disease-onset and in 76% of patients thereafter [35].

Treatment—Symptomatic therapy is often ineffective in MSA. More recently, droxidopa, a precursor of noradrenaline also known as L-threo-dops, has been investigated in phase 3 trials for neurogenic orthostatic hypotension (NOH) including MSA (NCT00782340). The results are not available yet, however, phase 2 results appear promising [36, 37]. Unfortunately, disease-modifying interventions are not available for MSA, although there are increasing efforts to identify candidate neuroprotective agents in the preclinical testbeds that have become available [2].

A recent clinical trial assessing the efficacy of minocycline in patients with MSA failed to demonstrate beneficial effects [38*]. Despite this disappointing finding, research into disease-modifying strategies has accelerated. Park et al. [39] reported evidence of neuroprotection mediated by mesenchymal stem cells (MSC) in the double toxin-double lesion MSA-P model. A prior open label MSC trial in a series of MSA-C patients claimed a disease-modifying effect [40]. Erythropoietin improved behavioural deficits and attenuated neurodegeneration in transgenic MSA mice with GCI-like inclusions and neurodegeneration [41]. Intriguingly, reduced expression of oligodendroglial GDNF was recently reported in cerebellar and frontal white matter of MSA brains as well as in transgenic MSA mice highlighting a further potential therapeutic target [4]. Currently, a number of phase 2 safety and efficacy trials are ongoing including rasagiline (NCT00977665), rifampicin (NCT01287221), lithium (NCT00997672), intravenous immunoglobulins (NCT00750867), and autologous MSC (NCT00911365).

Dementia With Lewy Bodies

Severe cognitive decline frequently emerges many years after the onset of parkinsonism in patients with PD dementia (PDD) [42]. In contrast, dementia with Lewy bodies (DLB), i.e.

dementia prior to the onset of parkinsonism [43], appears to be less common in movement disorder clinics. Both PDD and DLB share a similar distribution of Lewy bodies and neuronal loss.

Molecular pathogenesis—A recent study showed that more than 90% of α -synuclein aggregates in DLB cases were located in small deposits at the presynapses [44], suggesting that α -synuclein associated synaptic dysfunction drives neurodegeneration in DLB [45*]. Less is known about interactions between α -synuclein and other neuronal proteins, however, α -synuclein was shown to promote tau accumulation in vivo [46]. Intriguingly, a combined transgenic mouse model expressing human APP, human tau and human α -synuclein revealed that amyloid- β , tau, and α -synuclein interact synergistically in vivo, causing accelerated cognitive decline [47].

Genetics—DLB appears to be a sporadic disorder. Familial aggregation has rarely been reported, however, sequencing of candidate genes in a Belgian DLB pedigree failed to identify a pathogenic mutation [48]. A recent case-control study demonstrated that siblings of clinically diagnosed DLB patients are at increased risk of developing the disease [49].

Clinicopathological studies—There is considerable overlap between PDD and DLB [43], however, a study of 30 brains with Lewy body dementia revealed that only 2 of 13 PDD cases (15%) showed AD pathology in midbrain areas, whereas 12 of 17 DLB cases (71%) exhibited midbrain involvement [50]. Moreover, 4 of the DLB cases (24%) but none of the PDD cases exhibited amyloid pathology in the cerebellum [50]. Additionally, in a recent clinicopathological study all patients with mild cognitive impairment and RBD exhibited post-mortem confirmed Lewy body disease, with involvement of brainstem and cortical areas [51].

Diagnostic work-up—A recent DTI study in DLB patients showed increased amygdalar diffusivity in the absence of tissue loss, consistent with microvacuolation suggesting that DTI may be helpful in separating DLB from AD [52]. Cholinergic deficits seem to be important in the development of DLB as shown in a neuroimaging study analysing neurotransmitter changes using a voxel-based statistical parametric mapping and region of interest-based statistics [53*]. Moreover, this study demonstrated that both DLB and PDD patients share the same dopaminergic and cholinergic deficit profile in the brain [53*]. A meta-analysis determined confirmed the utility of cardiac MIBG scintigraphy as an accurate diagnostic marker separating DLB from other dementias with a pooled sensitivity of 98% and pooled specificity of 94% [54].

Treatment—A large prospective randomized placebo-controlled study reported significant improvement of clinical global impression of change in patients with either DLB or PDD with benefits being more prominent in the PDD subgroup [55*]. While memantine-mediated global improvement was replicated in mild to moderate DLB patients of another large multi-center trial, no beneficial effects were observed in the PDD group [56*].

Tauopathies

PSP and CBD are rare parkinsonian disorders resulting from pathological tau aggregation firmly placing these disorders within the enlarging spectrum of tauopathies including the frontotemporal dementias.

Progressive Supranuclear Palsy

During the last years infrequent variants due to PSP tau pathology have been separated from the “classical” syndrome (Richardson syndrome, RS) [57*]. These variants that challenge the concept of clinicopathologic PSP [58] include PSP-parkinsonism (PSP-P) [58], pure akinesia with gait freezing (PAGF) [59], CBS [60**, 61*], and progressive non-fluent aphasia (PSP-PNFA) [62].

Molecular pathogenesis—Data from human PSP brains and experimental models suggest that tau is hyperphosphorylated by kinases, leading to detachment from microtubules. Unbound phosphorylated tau, particularly as the 4R isoform, has an intrinsic propensity to form cytotoxic aggregates [63**]. Microtubules, in turn, are destabilized after detachment of tau and become depolymerized to tubulin-monomers, thereby losing their vital functions. Mitochondrial dysfunction appears to accelerate pathological tau aggregation [63**].

Genetics—Based on the current literature and with few exceptions, PSP can be considered a sporadic disorder. Vidal et al. [64] recently reported lack of familial aggregation 79 pairs of PSP cases and one first-degree relative matched for age, gender and living area for each PSP case. The pathogenic importance of tau aggregates in PSP is underpinned by the robust association of the H1 tau haplotype with PSP [65]. A recent genome-wide association study (GWAS) reported a major locus on chromosome 11p12-p11 which correlated with PSP disease risk [66]. Familial PSP is rare [67] and sometimes related to familial frontotemporal dementia with parkinsonism linked to chromosome 17 (FTDP-17) [68].

Clinical studies—A prospective natural history study determined a median survival of 8.0 years in a series of 197 PSP patients consistent with the rapid progression of this devastating disorder [69]. Male gender, older age at disease-onset and higher PSP rating scale scores were independent predictors of shorter survival [69]. A natural history study confirmed previous observations of high levels of cognitive impairment associated with PSP occurring in up to 50% of patients at early disease stages [18]. Furthermore, the cognitive profile characterized by frontal-executive dysfunction was similar to a control cohort of MSA patients [18]. Interestingly, impulse control disorders (ICDs) emerged during dopamine agonist treatment in 3 cases of pathologically proven PSP indicating that dopamine agonist induced behavioural side effects may not be limited to PD [70].

Clinicopathological studies—Due to the lack of specific biomarkers it has been suggested that the recently recognized clinical variants may be included under the generic term PSP reflecting rapidly progressive disease and similar pathology including 4R tau inclusions, tufted astrocytes, and coiled bodies [57*]. The regional differences in pathological severity almost certainly account for the clinical differences and logically

correlate with the different clinical features. The NINDS-SPSP were established 15 years ago focusing on the classic RS presentation [71]. Several clinical features such as visual hallucinations, drug-induced dyskinesias and autonomic dysfunction are uncommon in PSP-P and discriminate this subtype from other parkinsonian disorders including PD, DLB and MSA [72].

Diagnostic work-up—The diagnosis of PSP is primarily clinical. There is no consensus concerning additional investigations, however, neuropsychological testing and neuroimaging are often helpful [73, 74].

The diagnostic accuracy of brainstem MRI measurements such as the ratio between midbrain and pons areas (m/p-ratio), that between superior (SCP) and middle cerebellar peduncle (MCP) widths, and the MR parkinsonism index ($[\text{pons/midbrain}] \times [\text{MCP/SCP}]$, MRPI) was assessed in a study comparing different variants of PSP (i.e. PSP-P and PSP-RS) and PD [75]. While all measures were able to appropriately differentiate PSP-RS from PD, the m/p-ratio was the only measure found to distinguish PSP-P from PD [75]. Similarly, in a large cohort of 123 patients with neurodegenerative parkinsonian disorders including PSP, PD, and MSA-P, PSP cases had significantly higher MRPI values and smaller m/p-ratios compared to other groups [76*]. Furthermore, a voxel-based morphometry MRI approach found major anatomical differences between PSP-RS and PSP-P with additional grey matter loss within midbrain regions of patients with PSP-RS [77]. This finding was further supported by a study revealing thalamocortical atrophy as a defining feature of PSP-RS, however, there was no correlation between atrophy and the presence of any specific cardinal clinical feature [78]. Microstructural brain pathology in line with neuropathological studies was demonstrated in PSP patients by diffusion tensor imaging (DTI) subjected to tract-based spatial statistics analysis [79*]. A recent functional imaging study revealed impaired subcortical and brainstem cholinergic neurotransmission in PSP consistent with degeneration of cholinergic nuclei such as PPN [80]. The diagnostic relevance of these findings remains to be established in future studies. As previously mentioned, a computer-assisted image analysis was superior to a rater-based approach in classifying a β -CIT-SPECT image to either PD, MSA, PSP or healthy age-matched controls [27].

The role of CSF or blood markers is controversial. Aerts et al. [81] reported that CSF α -synuclein and tau levels did not differentiate PSP from PD and other APDs. However, a low ratio of a truncated and extended tau form in the CSF distinguished PSP from related disorders [82].

Treatment—Thus far, symptomatic therapy is limited and there are no established disease-modifying interventions. In this situation, palliative measures including physical, occupational and speech therapy remain the most important aspects in the management of patients with PSP. Recent insights into pathogenic mechanisms of PSP allowed the development and preclinical testing of promising compounds targeting key pathogenic events.

Experimental data in tauopathy models suggest that the inhibition of GSK-3 β might be a potential therapeutic target in PSP [63**]. Presently, several clinical trials with GSK-3 β

inhibitors such as lithium, valproic acid or NP031112 have been initiated or are ongoing in patients with PSP. The clinical study with lithium was terminated because of adverse events. NAPVSIQ (davunetide) is a neuroprotective peptide interacting with the microtubule cytoskeleton to improve microtubule function [83]. A clinical trial to test the effects of danuvetide in PSP is presently ongoing (NCT01056965). To improve mitochondrial dysfunction the short-term effects of coenzyme Q10 were studied in 21 PSP patients. Compared to placebo, this treatment significantly improved cerebral metabolism as measured by ^{31}P - and ^1H -MRS [84]. Several clinical measures including the PSP rating scale and the frontal assessment battery also improved. Whether long-term administration of coenzyme Q may impact on disease progression in PSP is currently investigated in a phase 3 trial (NCT00382824).

Corticobasal Degeneration

CBD is the least common neurodegenerative APD and may only be diagnosed post-mortem. The clinical presentation of CBD is variable and includes the CBS, PSP, progressive aphasia and frontotemporal dementia. However, CBD research is hampered by the rarity of the disorder patients being scattered over a large geographic area [1**].

Molecular pathogenesis—Multiple pathogenic mechanisms have been proposed in tauopathies in general, including mitochondrial dysfunction, oxidative stress, abnormal axonal transport, inflammation, and particularly disturbances in tau metabolism [85]. However, due to the complexity and rarity of CBD there have not been major recent advances.

Genetics—A recent study showed that the inheritance of the tau H1/H1 haplotype is associated with the severity of motor function but not age at onset and cognition in CBS patients [86]. Moreover, there was a trend towards shortened survival in the H1/H1 group which failed to reach significance, most likely due to sample size limitations [86]. Finally, frontotemporal dementia patients with defined tau mutations may also present with a CBD phenotype [87].

Clinicopathological studies—CBD is characterized by deposits of 4-repeat tau in cortical and striatal neurons and glia forming astrocytic plaques and by thread-like lesions affecting white and gray matter [88]. A recent clinicopathological study showed that only the minority of post-mortem confirmed CBD cases were diagnosed correctly in life (5 out of 19 cases) and that the clinical syndrome of CBS is not specific for CBD [60**]. Intriguingly, most of the pathologically confirmed CBD cases were characterized clinically by a PSP-like presentation with delayed onset of vertical supranuclear gaze palsy [60**]. TAR-DNA-binding protein 43 (TDP-43) inclusions that are distinctive of frontotemporal lobar degeneration with ubiquitin-positive inclusions (FTLD-U) may occur in a minority of CBD and PSP cases [89, 90], highlighting the overlap between CBD, PSP and FTLD-U.

Diagnostic work-up—Elevated levels of tau and phosphorylated tau protein may be found in patients with CBS, however, diagnostic accuracy seems to be poor [91]. Intriguingly, an AD-like CSF pattern was associated with early memory decline in CBS

patients according to a recent study [92]. Voxel-based morphometry may be used to predict underlying pathology in patients presenting with CBS as nicely shown by Whitwell and coworkers in a series of 24 patients [61*]. While widespread atrophy was associated with either FTLT or AD, CBD or PSP pathologies were characterized by focal atrophy predominantly involving premotor and supplemental motor areas [61*]. Cholinergic imaging using ^{11}C -N-methylpiperidin-4-yl acetate PET revealed decreased acetylcholinesterase activity in CBS and PSP patients, with CBS predominantly involving the paracentral region as well as frontal, parietal and occipital cortices [93].

Treatment—Since symptomatic therapy is largely ineffective in CBS patients there have been limited efforts to evaluate disease-modifying interventions. Lithium, a glycogen synthase kinase 3- β (GSK-3 β) inhibitor, ameliorated disease progression in transgenic tauopathy models [94] and is currently evaluated in a Phase II study combining patients with CBS and PSP (NCT00703677). In addition, the effects of NAPVSIPQ (davunetide) [95], a neuroprotective peptide that stimulates microtubule assembly and reduces tau phosphorylation are currently investigated in CBS (NCT01056965). Until specific biomarkers for underlying CBS pathologies are available recruitment of such patients into clinical trials seems warranted considering that most such patients will have an underlying tauopathy.

Conclusion and Future Perspectives

In recent years APDs have been increasingly recognized as important causes of parkinsonism and, thus, research into underlying pathogenic mechanisms, the aetiopathogenesis, diagnostic and progression markers, and novel interventional therapies has intensified. During the next few years we will see a further acceleration of research into genetics, molecular biology and neuroimaging of these disorders which will allow the development and assessment of disease-modifying strategies targeting key pathogenic events.

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References

1. Wenning GK, Tolosa E, Litvan I. Milestones in atypical and secondary parkinsonisms. *Mov Disord.* 2011 in press. [** Review of historical milestones and future perspectives in atypical parkinsonism.]
2. Stefanova N, Bucke P, Duerr S, Wenning GK. Multiple system atrophy: an update. *Lancet Neurol.* 2009 Dec; 8(12):1172–8. [PubMed: 19909915]
3. Wenning GK, Stefanova N, Jellinger KA, Poewe W, Schlossmacher MG. Multiple system atrophy: a primary oligodendrogliopathy. *Ann Neurol.* 2008 Sep; 64(3):239–46. [PubMed: 18825660]
4. Ubhi K, Rockenstein E, Mante M, Inglis C, Adame A, Patrick C, et al. Neurodegeneration in a transgenic mouse model of multiple system atrophy is associated with altered expression of

- oligodendroglial-derived neurotrophic factors. *J Neurosci.* 2010 May 5; 30(18):6236–46. [PubMed: 20445049]
5. Hasegawa T, Baba T, Kobayashi M, Konno M, Sugeno N, Kikuchi A, et al. Role of TPPP/p25 on alpha-synuclein-mediated oligodendroglial degeneration and the protective effect of SIRT2 inhibition in a cellular model of multiple system atrophy. *Neurochem Int.* 2010 Dec; 57(8):857–66. [PubMed: 20849899]
6. Goedert M, Clavaguera F, Tolnay M. The propagation of prion-like protein inclusions in neurodegenerative diseases. *Trends Neurosci.* 2010 Jul; 33(7):317–25. [PubMed: 20493564]
7. Stefanova N, Hainzer M, Stemberger S, Couillard-Despres S, Aigner L, Poewe W, et al. Striatal transplantation for multiple system atrophy—are grafts affected by alpha-synucleinopathy? *Exp Neurol.* 2009 Sep; 219(1):368–71. [PubMed: 19460374]
8. Hirohata M, Ono K, Morinaga A, Ikeda T, Yamada M. Cerebrospinal fluid from patients with multiple system atrophy promotes in vitro alpha-synuclein fibril formation. *Neurosci Lett.* 2011 Mar 10; 491(1):48–52. [PubMed: 21215793]
9. Scholz SW, Houlden H, Schulte C, Sharma M, Li A, Berg D, et al. SNCA variants are associated with increased risk for multiple system atrophy. *Ann Neurol.* 2009 May; 65(5):610–4. [PubMed: 19475667] [* First genome wide association study showing increased MSA disease risk with α -synuclein variants.]
10. Al-Chalabi A, Durr A, Wood NW, Parkinson MH, Camuzat A, Hult JS, et al. Genetic variants of the alpha-synuclein gene SNCA are associated with multiple system atrophy. *PLoS One.* 2009; 4(9):e7114. [PubMed: 19771175] [Confirmatory GWAS study demonstrating increased MSA disease risk associated with α -synuclein variants.]
11. Ross OA, Vilarino-Guell C, Wszolek ZK, Farrer MJ, Dickson DW. Reply to: SNCA variants are associated with increased risk of multiple system atrophy. *Ann Neurol.* 2010 Mar; 67(3):414–5.
12. Yun JY, Lee WW, Lee JY, Kim HJ, Park SS, Jeon BS. SNCA variants and multiple system atrophy. *Ann Neurol.* 2010 Apr; 67(4):554–5.
13. Hara K, Momose Y, Tokiguchi S, Shimohata M, Terajima K, Onodera O, et al. Multiplex families with multiple system atrophy. *ArchNeurol.* 2007; 64(4):545–51.
14. Wullner U, Schmitt I, Kammal M, Kretschmar HA, Neumann M. Definite multiple system atrophy in a German family. *J Neurol Neurosurg Psychiatry.* 2009 Apr; 80(4):449–50. [PubMed: 19289484]
15. Kollensperger M, Geser F, Ndayisaba JP, Boesch S, Seppi K, Ostergaard K, et al. Presentation, diagnosis, and management of multiple system atrophy in Europe: Final analysis of the European multiple system atrophy registry. *Mov Disord.* 2010 Oct 4. [** The largest clinical cohort of MSA patients showing serious under-treatment of autonomic dysfunction.]
16. Colosimo C, Morgante L, Antonini A, Barone P, Avarello TP, Bottacchi E, et al. Non-motor symptoms in atypical and secondary parkinsonism: the PRIAMO study. *J Neurol.* 2010 Jan; 257(1):5–14. [PubMed: 19669613]
17. Gilman S, Wenning GK, Low PA, Brooks DJ, Mathias CJ, Trojanowski JQ, et al. Second consensus statement on the diagnosis of multiple system atrophy. *Neurology.* 2008 Aug 26; 71(9):670–6. [PubMed: 18725592]
18. Brown RG, Lacomblez L, Landwehrmeyer BG, Bak T, Uttner I, Dubois B, et al. Cognitive impairment in patients with multiple system atrophy and progressive supranuclear palsy. *Brain.* 2010 Aug; 133(Pt 8):2382–93. [PubMed: 20576697]
19. Moreno-Lopez C, Santamaria J, Salamero M, Del Sorbo F, Albanese A, Pellecchia MT, et al. Excessive Daytime Sleepiness in Multiple System Atrophy (SLEEMSA Study). *Arch Neurol.* 2011 Feb; 68(2):223–30. [PubMed: 21320989] [* EMSA study demonstrating an increased frequency of RLS in MSA compared to PD.]
20. Claassen DO, Josephs KA, Ahlskog JE, Silber MH, Tippmann-Peikert M, Boeve BF. REM sleep behavior disorder preceding other aspects of synucleinopathies by up to half a century. *Neurology.* 2010 Aug 10; 75(6):494–9. [PubMed: 20668263]
21. Cochen De Cock V, Debs R, Oudiette D, Leu S, Radji F, Tiberge M, et al. The improvement of movement and speech during rapid eye movement sleep behaviour disorder in multiple system atrophy. *Brain.* 2011 Mar; 134(Pt 3):856–62. [PubMed: 21310729]

22. Schrag A, Sheikh S, Quinn NP, Lees AJ, Selai C, Mathias C, et al. A comparison of depression, anxiety, and health status in patients with progressive supranuclear palsy and multiple system atrophy. *Mov Disord.* 2010 Jun; 25(8):1077–81. *. [PubMed: 20535826]
23. Lee JY, Yun JY, Shin CW, Kim HJ, Jeon BS. Putaminal abnormality on 3-T magnetic resonance imaging in early parkinsonism-predominant multiple system atrophy. *J Neurol.* 2010 Dec; 257(12):2065–70. [PubMed: 20652301]
24. Minnerop M, Luders E, Specht K, Ruhlmann J, Schimke N, Thompson PM, et al. Callosal tissue loss in multiple system atrophy--a one-year follow-up study. *Mov Disord.* 2010 Nov 15; 25(15): 2613–20. [PubMed: 20623690]
25. Tha KK, Terae S, Yabe I, Miyamoto T, Soma H, Zaitu Y, et al. Microstructural white matter abnormalities of multiple system atrophy: in vivo topographic illustration by using diffusion-tensor MR imaging. *Radiology.* 2010 May; 255(2):563–9. [PubMed: 20413765]
26. Tang CC, Poston KL, Eckert T, Feigin A, Frucht S, Gudesblatt M, et al. Differential diagnosis of parkinsonism: a metabolic imaging study using pattern analysis. *Lancet Neurol.* 2010 Feb; 9(2): 149–58. [PubMed: 20061183] [* Observer-independent algorithm to classify metabolic image patterns to parkinsonian disorders]
27. Goebel G, Seppi K, Donnemiller E, Warwitz B, Wenning GK, Virgolini I, et al. A novel computer-assisted image analysis of [(123)I]beta-CIT SPECT images improves the diagnostic accuracy of parkinsonian disorders. *Eur J Nucl Med Mol Imaging.* 2010 Dec 21.
28. Iranzo A, Lomena F, Stockner H, Valldeoriola F, Vilaseca I, Salamero M, et al. Decreased striatal dopamine transporter uptake and substantia nigra hyperechogenicity as risk markers of synucleinopathy in patients with idiopathic rapid-eye-movement sleep behaviour disorder: a prospective study [corrected]. *Lancet Neurol.* 2010 Nov; 9(11):1070–7. [PubMed: 20846908]
29. Payoux P, Brefel-Courbon C, Ory-Magne F, Regragui W, Thalamas C, Balduyck S, et al. Motor activation in multiple system atrophy and Parkinson disease: a PET study. *Neurology.* 2010 Sep 28; 75(13):1174–80. [PubMed: 20876470]
30. Braune S, Reinhardt M, Schnitzer R, Riedel A, Lucking CH. Cardiac uptake of [123I]MIBG separates Parkinson's disease from multiple system atrophy. *Neurology.* 1999; 53(5):1020–5. [PubMed: 10496261]
31. Nagayama H, Ueda M, Yamazaki M, Nishiyama Y, Hamamoto M, Katayama Y. Abnormal cardiac [(123)I]-meta-iodobenzylguanidine uptake in multiple system atrophy. *Mov Disord.* 2010 Aug 15; 25(11):1744–7. [PubMed: 20645402]
32. Orimo S, Kanazawa T, Nakamura A, Uchihara T, Mori F, Kakita A, et al. Degeneration of cardiac sympathetic nerve can occur in multiple system atrophy. *Acta Neuropathol.* 2007 Jan; 113(1):81–6. [PubMed: 17089131]
33. Kikuchi A, Takeda A, Okamura N, Tashiro M, Hasegawa T, Furumoto S, et al. In vivo visualization of alpha-synuclein deposition by carbon-11-labelled 2-[2-(2-dimethylaminothiazol-5-yl)ethenyl]-6-[2-(fluoro)ethoxy]benzoxazole positron emission tomography in multiple system atrophy. *Brain.* 2010 Jun; 133(Pt 6):1772–8. [PubMed: 20430832] [* First PET study to demonstrate oligodendroglial synuclein pathology in MSA in vivo.]
34. Lipp A, Sandroni P, Ahlskog JE, Fealey RD, Kimpinski K, Iodice V, et al. Prospective differentiation of multiple system atrophy from Parkinson disease, with and without autonomic failure. *Arch Neurol.* 2009 Jun; 66(6):742–50. [PubMed: 19506134]
35. Bloch F, Pichon B, Bonnet AM, Pichon J, Vidailhet M, Roze E, et al. Urodynamic analysis in multiple system atrophy: characterisation of detrusorsphincter dyssynergia. *J Neurol.* 2010 Dec; 257(12):1986–91. [PubMed: 20683607]
36. Mathias CJ. L-dihydroxyphenylserine (Droxidopa) in the treatment of orthostatic hypotension: the European experience. *Clin Auton Res.* 2008 Mar; 18(Suppl 1):25–9. [PubMed: 18368304]
37. Kaufmann H. L-dihydroxyphenylserine (Droxidopa): a new therapy for neurogenic orthostatic hypotension: the US experience. *Clin Auton Res.* 2008 Mar; 18(Suppl 1):19–24. [PubMed: 18368303]
38. Dodel R, Spottke A, Gerhard A, Reuss A, Reinecker S, Schimke N, et al. Minocycline 1-year therapy in multiple-system-atrophy: effect on clinical symptoms and [(11)C] (R)-PK11195 PET

- (MEMSA-trial). *Mov Disord*. 2010 Jan 15; 25(1):97–107. [PubMed: 20014118] [* Negative multi-centre EMSA trial of Minocycline in MSA partly reflecting advanced disease in MSA patients.]
39. Park HJ, Bang G, Lee BR, Kim HO, Lee PH. Neuroprotective effect of human mesenchymal stem cells in an animal model of double toxin-induced multiple system atrophy-parkinsonism. *Cell Transplant*. 2010 Nov 5.
 40. Lee PH, Kim JW, Bang OY, Ahn YH, Joo IS, Huh K. Autologous mesenchymal stem cell therapy delays the progression of neurological deficits in patients with multiple system atrophy. *Clin Pharmacol Ther*. 2008 May; 83(5):723–30. [PubMed: 17898702]
 41. Kollensperger M, Krismer F, Pallua A, Stefanova N, Poewe W, Wenning GK. Erythropoietin is neuroprotective in a transgenic mouse model of multiple system atrophy. *Mov Disord*. 2011 Jan 6.
 42. Emre M, Aarsland D, Brown R, Burn DJ, Duyckaerts C, Mizuno Y, et al. Clinical diagnostic criteria for dementia associated with Parkinson's disease. *Mov Disord*. 2007 Sep 15; 22(12):1689–707. quiz 837. [PubMed: 17542011]
 43. McKeith IG, Dickson DW, Lowe J, Emre M, O'Brien JT, Feldman H, et al. Diagnosis and management of dementia with Lewy bodies: third report of the DLB Consortium. *Neurology*. 2005 Dec 27; 65(12):1863–72. [PubMed: 16237129]
 44. Totterdell S, Meredith GE. Localization of alpha-synuclein to identified fibers and synapses in the normal mouse brain. *Neuroscience*. 2005; 135(3):907–13. [PubMed: 16112475]
 45. Schulz-Schaeffer WJ. The synaptic pathology of alpha-synuclein aggregation in dementia with Lewy bodies, Parkinson's disease and Parkinson's disease dementia. *Acta Neuropathol*. 2010 Aug; 120(2):131–43. [PubMed: 20563819] [* Post-mortem study that highlights importance of synaptic synuclein aggregates in neuronal dysfunction.]
 46. Giasson BI, Forman MS, Higuchi M, Golbe LI, Graves CL, Kotzbauer PT, et al. Initiation and synergistic fibrillization of tau and alpha-synuclein. *Science*. 2003 Apr 25; 300(5619):636–40. [PubMed: 12714745]
 47. Clinton LK, Blurton-Jones M, Myczek K, Trojanowski JQ, LaFerla FM. Synergistic Interactions between Aβeta, tau, and alpha-synuclein: acceleration of neuropathology and cognitive decline. *J Neurosci*. 2010 May 26; 30(21):7281–9. [PubMed: 20505094]
 48. Meeus B, Nuytemans K, Crosiers D, Engelborghs S, Peeters K, Mattheijssens M, et al. Comprehensive genetic and mutation analysis of familial dementia with Lewy bodies linked to 2q35-q36. *J Alzheimers Dis*. 2010; 20(1):197–205. [PubMed: 20164589]
 49. Nervi A, Reitz C, Tang MX, Santana V, Piriz A, Reyes D, et al. Familial aggregation of dementia with Lewy bodies. *Arch Neurol*. 2011 Jan; 68(1):90–3. [PubMed: 21220678]
 50. Fujishiro H, Iseki E, Higashi S, Kasanuki K, Murayama N, Togo T, et al. Distribution of cerebral amyloid deposition and its relevance to clinical phenotype in Lewy body dementia. *Neurosci Lett*. 2010 Dec 3; 486(1):19–23. [PubMed: 20851165]
 51. Molano J, Boeve B, Ferman T, Smith G, Parisi J, Dickson D, et al. Mild cognitive impairment associated with limbic and neocortical Lewy body disease: a clinicopathological study. *Brain*. 2010 Feb; 133(Pt 2):540–56. [PubMed: 19889717]
 52. Kantarci K, Avula R, Senjem ML, Samikoglu AR, Zhang B, Weigand SD, et al. Dementia with Lewy bodies and Alzheimer disease: neurodegenerative patterns characterized by DTI. *Neurology*. 2010 Jun 1; 74(22):1814–21. [PubMed: 20513818]
 53. Klein JC, Eggers C, Kalbe E, Weisenbach S, Hohmann C, Vollmar S, et al. Neurotransmitter changes in dementia with Lewy bodies and Parkinson disease dementia in vivo. *Neurology*. 2010 Mar 16; 74(11):885–92. [PubMed: 20181924] [* Multi-tracer pet study demonstrating similar dopaminergic and cholinergic deficit profile in DLB and PDD]
 54. Treglia G, Cason E. Diagnostic Performance of Myocardial Innervation Imaging Using MIBG Scintigraphy in Differential Diagnosis between Dementia with Lewy Bodies and Other Dementias: A Systematic Review and a Meta-Analysis. *J Neuroimaging*. 2010 Nov 17.
 55. Aarsland D, Ballard C, Walker Z, Bostrom F, Alves G, Kossakowski K, et al. Memantine in patients with Parkinson's disease dementia or dementia with Lewy bodies: a double-blind, placebo-controlled, multicentre trial. *Lancet Neurol*. 2009 Jul; 8(7):613–8. [PubMed: 19520613] [* Important clinical trial showing global improvement in memantine-treated DLB and PDD patients.]

56. Emre M, Tsolaki M, Bonuccelli U, Destee A, Tolosa E, Kutzelnigg A, et al. Memantine for patients with Parkinson's disease dementia or dementia with Lewy bodies: a randomised, double-blind, placebo-controlled trial. *Lancet Neurol.* 2010 Oct; 9(10):969–77. [PubMed: 20729148] [* Important clinical trial showing global improvement in memantine-treated DLB patients but not in patients with PDD]
57. Williams DR, Lees AJ. Progressive supranuclear palsy: clinicopathological concepts and diagnostic challenges. *Lancet Neurol.* 2009 Mar; 8(3):270–9. [PubMed: 19233037] [* Excellent review that highlights the diversity of clinical presentations associated with PSP pathology.]
58. Williams DR, de Silva R, Paviour DC, Pittman A, Watt HC, Kilford L, et al. Characteristics of two distinct clinical phenotypes in pathologically proven progressive supranuclear palsy: Richardson's syndrome and PSP-parkinsonism. *Brain.* 2005 Jun; 128(Pt 6):1247–58. [PubMed: 15788542]
59. Williams DR, Holton JL, Strand K, Revesz T, Lees AJ. Pure akinesia with gait freezing: a third clinical phenotype of progressive supranuclear palsy. *Mov Disord.* 2007 Nov 15; 22(15):2235–41. [PubMed: 17712855]
60. Ling H, O'Sullivan SS, Holton JL, Revesz T, Massey LA, Williams DR, et al. Does corticobasal degeneration exist? A clinicopathological re-evaluation. *Brain.* 2010 Jul; 133(Pt 7):2045–57. [PubMed: 20584946] [** Clinicopathological study showing heterogeneity of neuropathological changes associated with CBS.]
61. Whitwell JL, Jack CR Jr, Boeve BF, Parisi JE, Ahlskog JE, Drubach DA, et al. Imaging correlates of pathology in corticobasal syndrome. *Neurology.* 2010 Nov 23; 75(21):1879–87. [PubMed: 21098403] [* Postmortem controlled VBM study in CBS patients demonstrating that in-vivo atrophy patterns predict underlying pathologies incl. CBS-CBD, CBS-AD, CBS-PSP and FTL D.]
62. Josephs KA, Petersen RC, Knopman DS, Boeve BF, Whitwell JL, Duffy JR, et al. Clinicopathologic analysis of frontotemporal and corticobasal degenerations and PSP. *Neurology.* 2006 Jan 10; 66(1):41–8. [PubMed: 16401843]
63. Stamelou M, de Silva R, Arias-Carrion O, Boura E, Hollerhage M, Oertel WH, et al. Rational therapeutic approaches to progressive supranuclear palsy. *Brain.* 2010 Jun; 133(Pt 6):1578–90. [PubMed: 20472654] [** Comprehensive review of therapeutic strategies in PSP]
64. Vidal JS, Vidailhet M, Derkinderen P, Tzourio C, Alperovitch A. Familial aggregation in atypical Parkinson's disease: a case control study in multiple system atrophy and progressive supranuclear palsy. *J Neurol.* 2010 Aug; 257(8):1388–93. [PubMed: 20625759]
65. Pittman AM, Myers AJ, Duckworth J, Bryden L, Hanson M, Abou-Sleiman P, et al. The structure of the tau haplotype in controls and in progressive supranuclear palsy. *Hum Mol Genet.* 2004 Jun 15; 13(12):1267–74. [PubMed: 15115761]
66. Melquist S, Craig DW, Huentelman MJ, Crook R, Pearson JV, Baker M, et al. Identification of a novel risk locus for progressive supranuclear palsy by a pooled genomewide scan of 500,288 single-nucleotide polymorphisms. *Am J Hum Genet.* 2007 Apr; 80(4):769–78. [PubMed: 17357082]
67. Rojo A, Pernaute RS, Fontan A, Ruiz PG, Honnorat J, Lynch T, et al. Clinical genetics of familial progressive supranuclear palsy. *Brain.* 1999 Jul; 122(Pt 7):1233–45. [PubMed: 10388790]
68. Rohrer JD, Paviour D, Vandrovcsa J, Hodges J, de Silva R, Rossor MN. Novel L284R MAPT Mutation in a Family with an Autosomal Dominant Progressive Supranuclear Palsy Syndrome. *Neurodegener Dis.* 2011; 8(3):149–52. [PubMed: 20838030]
69. Chiu WZ, Kaat LD, Seelaar H, Rosso SM, Boon AJ, Kamphorst W, et al. Survival in progressive supranuclear palsy and frontotemporal dementia. *J Neurol Neurosurg Psychiatry.* 2010 Apr; 81(4):441–5. [PubMed: 20360166]
70. O'Sullivan SS, Djamshidian A, Ahmed Z, Evans AH, Lawrence AD, Holton JL, et al. Impulsive-compulsive spectrum behaviors in pathologically confirmed progressive supranuclear palsy. *Mov Disord.* 2010 Apr 15; 25(5):638–42. [PubMed: 20213825]
71. Litvan I, Agid Y, Calne D, Campbell G, Dubois B, Duvoisin RC, et al. Clinical research criteria for the diagnosis of progressive supranuclear palsy (Steele-Richardson-Olszewski syndrome): report of the NINDS-SPSP international workshop. *Neurology.* 1996; 47(1):1–9. [PubMed: 8710059]

72. Williams DR, Lees AJ. What features improve the accuracy of the clinical diagnosis of progressive supranuclear palsy-parkinsonism (PSP-P)? *Mov Disord*. 2010 Feb 15; 25(3):357–62. [PubMed: 20108379]
73. Stamelou M, Knake S, Oertel WH, Hoglinger GU. Magnetic resonance imaging in progressive supranuclear palsy. *J Neurol*. 2011 Apr; 258(4):549–58. [PubMed: 21181185]
74. Colosimo C, Fabbrini G, Berardelli A. *Progressive Supranuclear Palsy Handbook of Atypical Parkinsonism*. Colosimo C, Riley DE, Wenning GK, editors Cambridge University Press; 2011.
75. Longoni G, Agosta F, Kostic VS, Stojkovic T, Pagani E, Stosic-Opincal T, et al. MRI measurements of brainstem structures in patients with Richardson's syndrome, progressive supranuclear palsy-parkinsonism, and Parkinson's disease. *Mov Disord*. 2011 Feb 1; 26(2):247–55. [PubMed: 21412831]
76. Hussl A, Mählke P, Scherfler C, Esterhammer R, Schocke M, Poewe W, et al. Diagnostic accuracy of the magnetic resonance Parkinsonism index and the midbrain-to-pontine area ratio to differentiate progressive supranuclear palsy from Parkinson's disease and the Parkinson variant of multiple system atrophy. *Mov Disord*. 2010 Oct 30; 25(14):2444–9. [PubMed: 20878992] [* Routine MR-based validation study of the midbrain/pontine-area ratio and the MR parkinson index showing smaller m/p ratio and higher MRPI values in PSP patients.]
77. Agosta F, Kostic VS, Galantucci S, Mesaros S, Svetel M, Pagani E, et al. The in vivo distribution of brain tissue loss in Richardson's syndrome and PSP-parkinsonism: a VBM-DARTEL study. *Eur J Neurosci*. 2010 Aug; 32(4):640–7. [PubMed: 20597976]
78. Schofield EC, Hodges JR, Macdonald V, Cordato NJ, Kril JJ, Halliday GM. Cortical atrophy differentiates Richardson's syndrome from the parkinsonian form of progressive supranuclear palsy. *Mov Disord*. 2010 Dec 13.
79. Knake S, Belke M, Menzler K, Pilatus U, Eggert KM, Oertel WH, et al. In vivo demonstration of microstructural brain pathology in progressive supranuclear palsy: a DTI study using TBSS. *Mov Disord*. 2010 Jul 15; 25(9):1232–8. [PubMed: 20222139] [* DTI revealing microstructural brain pathology in PSP.]
80. Gilman S, Koeppe RA, Nan B, Wang CN, Wang X, Junck L, et al. Cerebral cortical and subcortical cholinergic deficits in parkinsonian syndromes. *Neurology*. 2010 May 4; 74(18):1416–23. [PubMed: 20439843]
81. Aerts MB, Esselink RA, Abdo WF, Bloem BR, Verbeek MM. CSF alpha-synuclein does not differentiate between parkinsonian disorders. *Neurobiol Aging*. 2011 Jan 12.
82. Borroni B, Gardoni F, Parnetti L, Magno L, Malinverno M, Saggese E, et al. Pattern of Tau forms in CSF is altered in progressive supranuclear palsy. *Neurobiol Aging*. 2009 Jan; 30(1):34–40. [PubMed: 17709155]
83. Gozes I, Divinski I. NAP, a neuroprotective drug candidate in clinical trials, stimulates microtubule assembly in the living cell. *Curr Alzheimer Res*. 2007 Dec; 4(5):507–9. [PubMed: 18220512]
84. Stamelou M, Reuss A, Pilatus U, Magerkurth J, Niklowitz P, Eggert KM, et al. Short-term effects of coenzyme Q10 in progressive supranuclear palsy: a randomized, placebo-controlled trial. *Mov Disord*. 2008 May 15; 23(7):942–9. [PubMed: 18464278]
85. Ludolph AC, Kassubek J, Landwehrmeyer BG, Mandelkow E, Mandelkow EM, Burn DJ, et al. Tauopathies with parkinsonism: clinical spectrum, neuropathologic basis, biological markers, and treatment options. *Eur J Neurol*. 2009 Mar; 16(3):297–309. [PubMed: 19364361]
86. Litvan I, Chism A, Litvan J, Cambon A, Hutton M. H1/H1 genotype influences symptom severity in corticobasal syndrome. *Mov Disord*. 2010 Apr 30; 25(6):752–4.
87. Vandrovcsa J, Anaya F, Kay V, Lees A, Hardy J, de Silva R. Disentangling the role of the tau gene locus in sporadic tauopathies. *Curr Alzheimer Res*. 2010 Dec; 7(8):726–34. [PubMed: 20704554]
88. Dickson DW, Bergeron C, Chin SS, Duyckaerts C, Horoupian D, Ikeda K, et al. Office of Rare Diseases neuropathologic criteria for corticobasal degeneration. *J Neuropathol Exp Neurol*. 2002 Nov; 61(11):935–46. [PubMed: 12430710]
89. Yokota O, Davidson Y, Bigio EH, Ishizu H, Terada S, Arai T, et al. Phosphorylated TDP-43 pathology and hippocampal sclerosis in progressive supranuclear palsy. *Acta Neuropathol*. 2010 Jul; 120(1):55–66. [PubMed: 20512649]

90. Uryu K, Nakashima-Yasuda H, Forman MS, Kwong LK, Clark CM, Grossman M, et al. Concomitant TAR-DNA-binding protein 43 pathology is present in Alzheimer disease and corticobasal degeneration but not in other tauopathies. *J Neuropathol Exp Neurol*. 2008 Jun; 67(6): 555–64. [PubMed: 18520774]
91. Aerts MB, Esselink RA, Bloem BR, Verbeek MM. Cerebrospinal fluid tau and phosphorylated tau protein are elevated in corticobasal syndrome. *Mov Disord*. 2011 Jan; 26(1):169–73. [PubMed: 20836136]
92. Borroni B, Premi E, Agosti C, Alberici A, Cerini C, Archetti S, et al. CSF Alzheimer's disease-like pattern in corticobasal syndrome: evidence for a distinct disorder. *J Neurol Neurosurg Psychiatry*. 2011 Feb 22.
93. Hirano S, Shinotoh H, Shimada H, Aotsuka A, Tanaka N, Ota T, et al. Cholinergic imaging in corticobasal syndrome, progressive supranuclear palsy and frontotemporal dementia. *Brain*. 2010 Jul; 133(Pt 7):2058–68. [PubMed: 20558417]
94. Noble W, Planel E, Zehr C, Olm V, Meyerson J, Suleman F, et al. Inhibition of glycogen synthase kinase-3 by lithium correlates with reduced tauopathy and degeneration in vivo. *Proc Natl Acad Sci U S A*. 2005 May 10; 102(19):6990–5. [PubMed: 15867159]
95. Matsuoka Y, Jouroukhin Y, Gray AJ, Ma L, Hirata-Fukae C, Li HF, et al. A neuronal microtubule-interacting agent, NAPVSIPQ, reduces tau pathology and enhances cognitive function in a mouse model of Alzheimer's disease. *J Pharmacol Exp Ther*. 2008 Apr; 325(1):146–53. [PubMed: 18199809]

Key Points

- Important genetic advances in APDs during the last years include the discovery of variants in the synuclein and tau gene with increased disease risk for MSA and PSP.
- The diagnostic accuracy and surrogate monitoring of disease activity has improved with the aid of advanced neuroimaging tools.
- Preclinical evidence, particularly in MSA models, stimulates further research into disease-modifying strategies in APD patients.