

## Milestones in Atypical and Secondary Parkinsonisms

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**ABSTRACT:** During the last decades, atypical parkinsonian disorders such as multiple system atrophy, dementia with Lewy bodies, progressive supranuclear palsy, and corticobasal degeneration along with secondary parkinsonian disorders have been increasingly recognized as important causes of parkinsonism. Although treatment options are largely limited to date, remarkable progress has occurred through advances in the fields of molecular biology and diagnostic neuroimaging, resulting in intense preclinical

drug discovery programs. Early-investigation-assisted clinical diagnosis has become more crucial than ever because disease-modifying therapies will hopefully become available within this decade. © 2011 Movement Disorder Society

**Key Words:** multiple system atrophy; dementia with Lewy bodies; progressive supranuclear palsy; corticobasal degeneration; secondary parkinsonism

The majority of patients with parkinsonism have idiopathic Parkinson's disease (PD). However, parkinsonian patients with disorders other than PD are increasingly recognized. Some of them have been labeled "Parkinson-plus" because of additional ("plus") features beyond the classic PD presentation. More recently, the term *atypical parkinsonian disorders* (APDs) has been coined comprising multiple system atrophy (MSA), dementia with Lewy bodies (DLB), progressive supranuclear palsy (PSP), and corticobasal degeneration (CBD); see Table 1. Remarkably, the APDs were all reported during the 1960s. Although levodopa-unresponsive parkinsonism and some of the associated atypical features (Table 2) had emerged as clinical hallmarks, recognition of APDs among movement disorders neurologists was limited until the

1980s, partly reflecting the lack of predictive diagnostic criteria at that time. The pattern of neuronal loss and signature lesions was established, and it is still required for a definite diagnosis of the APDs; however, disease-specific proteinopathy, defined by alpha-synuclein, tau, progranulin, and tata box inclusion pathology, was unknown. Structural and functional neuroimaging of parkinsonian disorders was in its infancy. Insights into the etiopathogenesis of APDs were grossly limited, and the epidemiology of the APDs was unknown. Historical milestones in the nosology and further understanding of these APDs are summarized in Table 3. The APDs need to be distinguished from other causes of parkinsonism including secondary parkinsonism (see below).

### Advances in the Past 25 Years

#### Atypical Parkinsonian Disorders

##### **Multiple System Atrophy (MSA)**

**Clinical.** MSA is a sporadic neurodegenerative disorder characterized clinically by various combinations of autonomic, cerebellar, parkinsonian, and pyramidal features.<sup>1</sup> The term was introduced in 1969<sup>2</sup>; however, cases of MSA were previously reported under the rubrics of olivopontocerebellar atrophy (OPCA),<sup>3</sup>

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**TABLE 1.** Classification of APDs according to protein aggregation

Synucleinopathies	Tauopathies
Parkinson's disease dementia	Progressive supranuclear palsy Richardson's syndrome PSP-parkinsonism Pure akinesia Corticobasal syndrome
Dementia with Lewy bodies	Corticobasal degeneration Richardson's syndrome Corticobasal syndrome Frontotemporal dementia Progressive nonfluent aphasia
Multiple system atrophy Parkinsonian variant (MSA-P) Cerebellar variant (MSA-C)	

Shy Drager syndrome (SDS)<sup>4</sup> and striatonigral degeneration (SND).<sup>5</sup> Major clinical advances in the last 25 years have been the introduction of clinical diagnostic criteria with a subdivision according to the predominance of parkinsonism versus ataxia into MSA-P and MSA-C,<sup>6–8</sup> the development and validation of a unified MSA rating scale (UMSARS),<sup>9</sup> and the development of functional and structural neuroimaging tools for early diagnosis and progression monitoring.<sup>10</sup>

**Pathology.** The breakthrough discovery of (oligodendro)glial cytoplasmic inclusions (GCIs) in MSA brains by Papp and colleagues<sup>11</sup> provided a neuropathological basis for considering heterogenous clinicopathological presentations such as OPCA, SDS, and SND as a distinctive clinicopathological entity. Almost 10 years later, alpha-synuclein was recognized as a key constituent of GCIs linking MSA closely with Lewy body disorders (LBDs) such as pure autonomic failure (PAF), PD, and DLB.<sup>12</sup> However, in contrast to the neuronal inclusion pathology of LBDs, there is accumulating evidence of a primary oligodendroglial pathology in MSA.<sup>13</sup>

**Epidemiologic.** Despite increasing clinical recognition of MSA, remarkably little good-quality evidence exists on its epidemiology. The few existing studies suggest a prevalence rate below 5 and an incidence rate below 1 in 100,000.<sup>14–16</sup> Other than possible rare exposures of pesticides and related chemicals, there is little to go on for specific environmental clues.<sup>17–19</sup> Positive findings with occupational exposures may reflect publication bias, and negative studies may simply be underpowered. Future research must either use a multicenter approach or use standardized methods to enable future meta-analyses of results.

**Genetic.** Research efforts in the last 2 decades have identified several genes associated with an increased risk in MSA, first and foremost the *SNCA* gene, coding for  $\alpha$ SYN, the major component of glial cyto-

plasmic inclusions (GCIs), the hallmark of the disease.<sup>20,21</sup> Moreover, genes involved in oxidative stress, mitochondrial dysfunction, inflammatory processes, PD, and ataxia-related genes have been analyzed by various methods, including genome-wide association studies (GWAS), to determine a genetic susceptibility spectrum for MSA.<sup>22</sup> To date, a disease-causing gene has not been identified, and the pathogenic (and even the physiological) role of proteins or pathways linked to human MSA and their encoding genes is far from clear.

**Pathogenic.** The major recent insights into MSA pathogenesis are derived from animal experimental and neuropathological studies suggesting oligodendroglial  $\alpha$ -synucleinopathy as a primary trigger of MSA-like neurodegeneration.<sup>13</sup> Transgenic mice with targeted overexpression of human  $\alpha$ -synuclein under the control of specific oligodendroglial promoters have replicated

**TABLE 2.** Selected features suggestive of atypical parkinsonism (modified from reference 156)

<b>Motor</b>	Rapid disease progression Early instability and falls Early freezing Poor response to levodopa Stimulus-sensitive myoclonus Orofacial dystonia (spontaneous or levodopa-induced) Camptocormia Pisa syndrome Disproportionate antecollis; retrocollis Rocket sign Procerus (corrugator supercilii) sign Pyramidal signs Cerebellar signs Early dysarthria and dysphagia Contractures Severe fixed-limb dystonia Predominantly axial rigidity
<b>Autonomic</b>	Impotence/decreased genital sensitivity in women Early and severe orthostatic hypotension Absence of heart rate increase on standing Early and severe urinary incontinence/incomplete bladder emptying Fecal incontinence Progressive anhidrosis Nocturnal stridor Cold hands sign Extremity circulatory congestion
<b>Oculomotor</b>	Slowing of vertical saccades Difficulty initiating saccades Supranuclear gaze palsy Square wave jerks Gaze-evoked and positional downbeat nystagmus
<b>Cognitive and neurobehavioral</b>	Early and severe frontal dementia Visual hallucinations not induced by medication Ideomotor apraxia Primary progressive aphasia Cortical sensory loss Sensory and/or visual neglect

**TABLE 3.** Historical milestones in APDs

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<b>MSA</b>	
1900	Cerebellar presentation (Dejerine and Thomas <sup>3</sup> )
1960	Autonomic presentation (Shy and Drager <sup>4</sup> )
1961	Parkinson presentation (Adams et al <sup>5</sup> )
1969	Proposal of MSA as “umbrella” term (Graham and Oppenheimer <sup>2</sup> )
1989	Glial cytoplasmic inclusions as cell marker of MSA (Papp et al <sup>11</sup> )
1989	First set of diagnostic criteria (Quinn <sup>6</sup> )
1998	MSA is an $\alpha$ -synucleinopathy (Spillantini et al <sup>12</sup> )
1998	Consensus diagnostic criteria (Gilman et al <sup>7</sup> )
1999	Foundation of the European MSA Study Group ( <a href="http://www.emsa-sg.org">http://www.emsa-sg.org</a> )
2004	Unified MSA Rating Scale (Wenning et al <sup>9</sup> )
2005	Transgenic MSA mouse models (Stefanova et al <sup>157</sup> )
2005	North American MSA Study Group formed (Gilman et al <sup>158</sup> )
2008	Revised consensus diagnostic criteria (Gilman et al <sup>8</sup> )
2009	SNCA variants increase the risk for MSA (Scholz et al, <sup>20</sup> Al-Chalabi et al <sup>21</sup> )
2009	NNIPPS trial of riluzole in MSA (and PSP) patients (Bensimon et al <sup>29</sup> )
2010	EMSA/NAMSA trial of rasagiline (Poewe et al <sup>159</sup> )
2010	NAMSA trial of rifampicine (Gilman and Low, personal communication)
2010	GWAS study launched (Sailer and Scholz, personal communication)
<b>DLB/PDD</b>	
1961	First report of DLB (Okazaki et al <sup>33</sup> )
1990	Lewy body variant of Alzheimer’s disease (Hansen et al <sup>34</sup> )
1993	Delineation of neuropathology in Lewy body disease (Kosaka <sup>160</sup> )
1996	Diagnostic criteria for DLB (McKeith et al <sup>36</sup> )
1998	$\alpha$ -Synuclein is a sensitive marker of DLB and PDD (Takeda et al <sup>161</sup> )
1998	Hereditary forms of DLB and PDD (Muentner et al <sup>162</sup> )
2000	Efficacy of rivastigmine in DLB (McKeith et al <sup>55</sup> )
2004	LRRK2 mutations in DLB (Zimprich et al <sup>44</sup> )
2004	Efficacy of rivastigmine in PDD (Emre et al <sup>163</sup> )
2005	Revision of diagnostic criteria for DLB (McKeith et al <sup>31</sup> )
2006	Glucocerebrosidase mutations in DLB (Goker-Alpan et al <sup>45</sup> )
2007	Diagnostic criteria for PDD (Emre et al <sup>164</sup> )
<b>PSP</b>	
1964	First clinicopathological report of PSP (Steele et al <sup>165</sup> )
1986	Filamentous tau is present in PSP brains (Pollock et al <sup>166</sup> )
1987	Pure akinesia (Imai et al <sup>167</sup> )
1987	First clinical diagnostic criteria for PSP (Lees <sup>168</sup> )
1994	Standardization of the neuropathologic criteria for PSP (Hauw et al <sup>72</sup> )
1996	Validation of neuropathologic criteria for PSP (Litvan et al <sup>65</sup> )
1996	NINDS-SPSP diagnostic criteria (Litvan et al <sup>66</sup> )
1998	PSP is a 4-repeat tauopathy (Mailliot et al <sup>169</sup> )
1998	PSP is association with a repeated tau polymorphism (Conrad et al <sup>170</sup> )
1999	PSP is associated with the MAPT H1 haplotype (Baker et al, <sup>171</sup> Bonifati et al <sup>172</sup> )
1999	PSP-like cluster on Guadeloupe linked to <i>Annona muricata</i> , a tropical fruit (Caparros-Lefebvre et al <sup>173</sup> )
2005	Various PSP phenotypes (Williams et al <sup>174</sup> )
2007	Identification of a second major locus on chromosome 11 associated with PSP (Melquist et al <sup>80</sup> )
2009	NNIPPS trial of riluzole in PSP (and MSA) patients (Bensimon et al <sup>29</sup> )
2010	Ongoing biological experimental trials in PSP
2010	First GWAS in PSP completed (Höglinger et al, personal communication)
2010	NIH sponsored study of environmental and genetic risk factors in PSP (Litvan et al, personal communication)
<b>CBD</b>	
1968	First report of CBD (Rebeiz et al <sup>175</sup> )
1990	Premortem diagnosis of CBD (Riley et al <sup>176</sup> )
1994	Clinical diagnostic criteria (Lang et al <sup>177</sup> )
1999	Clinicopathological heterogeneity (Boeve et al, <sup>178</sup> Kertesz et al <sup>179</sup> )
2001	PSP and CBD share a tau haplotype (Houlden et al <sup>79</sup> )
2002	Standardization and validation of neuropathological criteria (Dickson et al <sup>92</sup> )
2009	First multicenter experimental therapeutic study in CBD
2010	First GWAS study of CBD launched

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features of GCI-like inclusions, mitochondrial dysfunction, and enhanced vulnerability toward exogenous oxidative stress, neurodegeneration, and astro- and microgliosis.<sup>23–26</sup>

These animal models have provided invaluable test beds for the screening of candidate neuroprotective therapies and have led to several interventional trials.<sup>22</sup>

**Diagnostic tests.** The greatest singular advance in diagnostic testing for MSA within the last 2 decades has been the introduction of conventional MR imaging,<sup>27</sup> whereas the impact of other tools such as functional imaging (PET/SPECT) and autonomic function, neuroendocrine, or sphincter EMG testing, although often equally valuable, has been more limited to a few distinguished sites. More recently, advanced MR techniques such as diffusion-weighted imaging (DWI), diffusion tensor imaging (DTI), MR spectroscopy, and volumetry have been explored in MSA patients with high-field scanners, further improving the diagnostic accuracy and increasing the number of candidate surrogate markers.<sup>10</sup>

**Therapeutic.** In general, therapeutic management has remained unchanged over the last 25 years. Established symptomatic strategies comprise antiparkinsonian drugs or pharmacological interventions aimed at orthostatic and urogenital symptoms. Beneficial effects are infrequent and often poorly sustained because of disease progression. However, recent insights into the pathogenesis and the formation of international networks such as EMSA-SG (<http://www.emsa-sg.org>), JAMSAC, and NAMSAC-SG have led to a series of neuroprotection trials.<sup>28–30</sup> Although all of them were negative, invaluable insights into trial methodology including selection of surrogate markers are likely to stimulate future trial activities in MSA that may be considered a clinical test bed for PD.

### **Dementia with Lewy bodies (DLB)**

**Clinical.** Dementia with Lewy bodies (DLB) is a neurodegenerative dementia in older people, and it has been recognized more widely since the early '90s. There is considerable overlap with Parkinson's disease dementia (PDD), a more common entity characterized by delayed-onset cognitive decline emerging at least 1 year after motor onset.<sup>31</sup> The major clinical advance in the last 25 years has been the introduction of clinical diagnostic criteria with a subdivision of DLB and PDD.<sup>31,32</sup>

**Pathology.** In 1961, Okazaki et al<sup>33</sup> reported Lewy bodies (LBs) in the cerebral cortex of 2 patients with PD and atypical dementia. Although subsequent cases of diffuse Lewy body disease were published, the condition was initially considered rare. In the late 1980s, with greater awareness of cortical LBs and the development of more sensitive staining methods, several groups reported finding cortical LBs in 15%–25% of elderly demented patients.<sup>34,35</sup> Stimulated by these findings, McKeith et al<sup>36</sup> first proposed clinicopathological diagnostic criteria (that have been revised since to include alpha-synuclein immunostaining for LBs<sup>31</sup>) assuming that DLB is distinguishable from other

causes of dementia in life. Most DLB cases show some degree of Alzheimer's disease (AD)-like pathology, particularly diffuse senile plaques and limbic neurofibrillary tangles. This overlap between DLB and AD pathology, combined with the lack of universally accepted pathological diagnostic criteria for either disorder, has resulted in an ongoing controversy over the relationship between the 2 disorders.

**Epidemiologic.** DLB is widely regarded as the second most common cause of neurodegenerative dementia after AD.<sup>37</sup> However, there is only limited evidence to support this assumption because most of the available epidemiological studies suffer from inherent bias from reliance on brain bank or clinical case registries. Only a few well-designed studies suggest frequency rates between 11% and 22% of demented subjects in the community.<sup>38–40</sup> Although exposures of pesticides and related chemicals may be important risk factors in DLB similar to PD or MSA, no studies have been reported at present.

**Genetic.** In the past few years, mutations have been identified in the genes encoding alpha-synuclein,<sup>41–43</sup> leucine-rich repeat kinase 2,<sup>44</sup> and glucocerebrosidase<sup>45</sup> in some patients with DLB. Furthermore, a novel locus for familial DLB has been mapped to chromosome 2q35–q36.<sup>46</sup> Collectively, these discoveries highlight a substantial overlap between the known genetic determinants of PD and DLB, as well as the presence of profound etiologic heterogeneity in Lewy body disorders.

**Pathogenic.** DLB is a neuronal  $\alpha$ -synucleinopathy resulting in dysfunction of synaptic vesicles in presynaptic terminals. Recent progress suggests that the aggregate formation of alpha-synuclein is cytoprotective and that its precursor oligomer (protofibril) may be cytotoxic. The catechol-derived quinones are the candidate molecules that facilitate the oligomer formation of alpha-synuclein. Furthermore, the cellular membranes have been shown to be the primary targets injured by mutant alpha-synucleins, and mitochondrial dysfunction seems to be an initial step in the neuronal death.<sup>47</sup> More recent evidence suggests that misfolded  $\alpha$ -synuclein can transfer between cells and, once transferred into a new cell, can act as a seed that recruits endogenous  $\alpha$ -synuclein, leading to formation of larger aggregates similar to the prion disorders. Therefore, strategies aimed at prevention of cell-to-cell transfer of  $\alpha$ -synuclein could retard progression of symptoms in synucleinopathies such as PD or DLB.<sup>48</sup>

**Diagnostic tests.** The McKeith criteria for a diagnosis of DLB have been established as the gold standard over the last 15 years because of their high sensitivity

and specificity.<sup>31</sup> The criteria are primarily based on clinical and neuropsychological features; however, nigrostriatal denervation as shown by dopamine transporter imaging is allowed as a supportive feature. Numerous studies have addressed the diagnostic potential of CSF studies as well as advanced MR and functional imaging in patients with clinically probable DLB<sup>49–53</sup>; however, whether these techniques facilitate the recognition of early suspected cases remains unknown. Finally,  $\alpha$ -synuclein imaging may serve as both diagnostic and surrogate markers; however, technical hurdles are still to be overcome to permit successful in vivo imaging of  $\alpha$ -synuclein pathology in the diseased DLB brain.<sup>54</sup>

**Therapeutic.** Managing DLB patients is challenging because of the relentless cognitive and motor decline frequently associated with psychotic disorders. However, several level 1 trials provide a solid framework for therapeutic intervention in DLB. The treatment of choice for DLB-associated dementia is cholinesterase inhibitors (ChEIs) such as rivastigmine or donepezil.<sup>55,56</sup> ChEIs improve not only cognitive functioning but also reduce productive-psychotic symptoms. More recently, memantine has also been shown to improve the general functioning of DLB patients (Aarsland, 2009; Emre, 2010).<sup>57,58</sup> Anticholinergics and dopamine agonists should be tapered and discontinued, and levodopa therapy should be optimized. If psychotic features do not respond to anticholinesterase inhibitors, atypical neuroleptics such as quetiapine are usually administered but have not been shown to be beneficial in controlled trials.<sup>59</sup> Clozapine trials have shown beneficial effects but require regular blood counts.<sup>60</sup> Disease-modifying therapies for  $\alpha$ -synucleinopathies are urgently required, and multiple targets are currently being explored in PD models.<sup>61</sup> The overlapping features of PD, PDD, and DLB suggest that interventional PD therapies may also be relevant for DLB and vice versa. Thus, drug discovery in DLB may serve as an accelerating template for novel PD therapies.

### **Progressive Supranuclear Palsy (PSP)**

**Clinical.** PSP is a common atypical neurodegenerative parkinsonian disorder.<sup>16,62,63</sup> This sporadic disease with onset in the middle sixties was first described as a distinct clinicopathological entity by Steele, Richardson, and Olszewski in the early 1960s.<sup>64</sup> The patients described, most recently labeled as PSP-Richardson syndrome, presented with early postural instability, vertical supranuclear gaze palsy, severe axial levodopa-unresponsive, akinetic-rigid syndrome, early pseudobulbar dysarthria and dysphagia, and early severe frontal dysfunction. Several clinical diagnostic criteria were developed to diagnose this most common phenotypic presentation<sup>65</sup>; the most commonly used

are the NINDS-SPSP criteria,<sup>66</sup> which are highly specific. The relatively low sensitivity of this set of criteria likely reflects the varied PSP phenotypes. Postural instability manifesting as early unexplained falls<sup>67</sup> is the most frequent symptom at onset in patients with the PSP-Richardson syndrome. On the other hand, vertical supranuclear gaze palsy rarely presents at symptom onset. Evaluation of the speed of the saccades (rapid eye movement between 2 stimuli) and detection of slowing of vertical saccades allows an earlier diagnosis.

Approximately one third of patients with PSP develop the PSP-parkinsonism phenotype, asymmetric parkinsonism initially responding to levodopa<sup>68</sup>; rarely, patients with PSP present with a pure akinetic syndrome characterized by freezing of gait or isolated frontotemporal lobe dementia or corticobasal syndrome (see below).<sup>69</sup> Accurate diagnosis, important for management, prognosis, and research participation, relies on a detailed history and examination including evaluation of speed of saccades, cognition, behavior, motor, praxis, and autonomic functions. In general, symptoms and signs apparent early in the course of PSP progress steadily, but prognosis depends on the phenotype. Patients presenting with the PSP-Richardson phenotype have a shorter survival than those with PSP-parkinsonism or pure akinetic syndrome.

Major clinical advances in the last 25 years have been the development and validation of clinical diagnostic criteria,<sup>70</sup> recognition of the heterogeneity of phenotypes,<sup>69</sup> and development and validation of a PSP rating scale.<sup>71</sup>

**Pathology.** There are no biological markers for PSP, and pathology constitutes the diagnostic gold standard for its diagnosis. Over the past 25 years major progress has been made in standardizing and validating neuropathological diagnostic criteria<sup>66,72</sup> and better understanding its neurobiology. In PSP tau aggregates in neurons forming the neurofibrillary tangles and in glia as tufted astrocytes and oligodendroglial inclusions. The various clinical PSP phenotypes reflect the varying anatomical distribution of tau pathology. In PSP-Richardson syndrome there are abundant neurofibrillary tangles and/or neuropil threads in the striatum, pallidum, subthalamic nucleus, substantia nigra, oculomotor complex, periaqueductal gray, superior colliculi, basis pontis, dentate nucleus, and prefrontal cortex.<sup>70,72</sup> The brains of patients with frontotemporal dementia and corticobasal syndrome have greater cortical pathology than those with Richardson syndrome, and those with PSP-parkinsonism and pure akinesia have more severe degeneration in basal ganglia nuclei.<sup>73</sup>

The pathological tau in PSP is composed of aggregates of 4 repeat (E10+) isoforms. Neurochemical studies show that the degenerative process in PSP

involves dopaminergic neurons that innervate the striatum and form the nigrostriatal dopamine system, as well as cholinergic and GABAergic efferent neurons in the striatum and other basal ganglionic and brain stem nuclei, thereby explaining the lack or transient nature of the levodopa response.<sup>74</sup>

*Epidemiologic.* Over the past 25 years, clinicians have learned to better recognize PSP, but it remains an underdiagnosed disorder. Two population-based prevalence studies conducted in the United Kingdom and a general population-based survey in Olmsted County, Minnesota, using diagnostic criteria for PSP-Richardson syndrome estimated a prevalence of 6.0–6.4/100,000 for PSP-Richardson syndrome.<sup>16,62,63</sup> Its incidence increases with age, from 1.7 cases per 100,000 per year at 50–59 years to 14.7 per 100,000 per year at 80–99 years.<sup>16,75</sup>

There have been no studies determining the prevalence or incidence of patients with the other PSP phenotypes. An increased recognition of the various PSP phenotypes by neurologists and non-neurologists and better study designs and case definitions will lead to higher incidence and prevalence estimates of this disease.

*Genetic.* There have been major advances in the understanding of the genetics of PSP. Familial PSP cases are very infrequent<sup>76</sup> and rarely a result of familial frontotemporal dementia, with parkinsonism linked to chromosome 17 (FTDP-17) mutated tau or non-tau genes.<sup>77</sup> On the other hand, common extended variations in the tau gene (*MAPT*) that define the H1 and H2 haplotype strongly influence PSP risk. Multiple studies have confirmed that PSP is strongly associated with the H1 haplotype.<sup>78,79</sup> In addition to a robust association with the *MAPT* H1 haplotype, a pooling-based GWAS found a major locus on chromosome 11p12–p11, further narrowed to a single haplotype block that contains DNA damage-binding protein 2 and lysosomal acid phosphatase 2 genes.<sup>80</sup> Moreover, a recently completed multicenter GWAS analysis including more than 1000 autopsy-confirmed PSP cases on phase I and more than 1000 clinically diagnosed patients fulfilling the NINDS-SPSP criteria on phase II identified additional genes such as those related to the Golgi endoplasmic reticulum that will help disentangle the pathogenesis of this disease and will allow the development of rational biologic therapeutic approaches that may slow disease progression.

*Pathogenic.* The breakthrough observation that coding and splice-site mutations in the tau gene cause FTDP-17 demonstrates that tau dysfunction is sufficient to induce neurodegeneration.<sup>81–84</sup> In addition to genetic

factors, inflammation and oxidative injury lead to aggregation of tau, affecting different neuronal populations and manifesting as various phenotypic presentations. Further characterization of the cascade of events involved in tau dysfunction and neurodegeneration will be critical to ultimately developing the most beneficial therapies.

*Diagnostic tests.* Currently it is unclear if ancillary studies would improve diagnostic accuracy and, if so, which diagnostic test would have higher positive predictive value, be less invasive, and more economic. Thus far, studies evaluating the overall concentration of tau (phosphorylated and not phosphorylated) in cerebrospinal fluid (CSF) have not been useful in appropriately differentiating PSP from other disorders. However, a low ratio of a truncated and an extended tau form in the CSF (tau ratio, 33/55 kDa) has been reported to distinguish PSP from related disorders.<sup>85</sup>

Over the past 25 years neuroimaging, particularly magnetic resonance imaging (MRI), has been shown to be helpful in the differential diagnosis of PSP from other related disorders, but ultimately, the patterns reflect the underlying topographical involvement. Thinning of the quadrigeminal plate, particularly in its superior part, better seen in sagittal MRI sections, and dilation of the third ventricle support a diagnosis of PSP-Richardson. Increased echogenicity in the striatum, low echogenicity in the substantia nigra, and an increased third ventricle size are the main transcranial ultrasonography features that differentiate PSP-Richardson syndrome from PD and other atypical parkinsonian disorders.<sup>86</sup> Novel techniques such as diffusion tensor imaging may help to better understand the PSP microstructure, but the development of specific PET tau radiotracers is what will be more diagnostically meaningful. The combination of biologic markers is likely to increase diagnostic accuracy, but only use of neuropathology as a diagnostic gold standard will reveal the true usefulness of these markers.

*Therapeutic.* There are no therapies that can slow or stop PSP progression. However, as a result of better knowledge of the pathogenesis of PSP, successful therapeutic approaches in 4-repeat tau-transgenic animal models are being translated into experimental biologic therapies.<sup>87</sup> Several ongoing double-blind placebo-controlled experimental trials have attempted to hinder abnormal aggregation of microtubule-associated protein tau through the use of GSK  $\beta$  inhibitors such as tideglusib (NP031112), cytoskeleton stabilizers such as davunetide (AL 108), and free-radical scavengers and enhancers of metabolism such as coenzyme Q-10. Translation from the bench to the clinic usually is not straightforward; side effects led to the discontinuation of a multicenter lithium trial, and unforeseen sponsor

difficulties led to the discontinuation of a creatine, pyruvate, and niacinamide pilot study.

Not surprisingly, in view of the widespread involvement of dopaminergic and nondopaminergic neurotransmitter systems in PSP, neurotransmitter replacement therapies have been disappointing.<sup>88,89</sup> In clinical practice, palliative measures including physical, occupational, and speech therapy significantly help the management of PSP patients.

### **Corticobasal Degeneration (CBD)**

**Clinical.** Corticobasal degeneration (CBD) is the least common neurodegenerative atypical parkinsonian disorder. CBD patients usually present in the sixth or seventh decade with various clinical phenotypes including corticobasal syndrome, primary progressive nonfluent aphasia, and the behavioral variant of frontotemporal dementia. Patients with corticobasal syndrome usually present with a *unilateral* ideomotor or limb kinetic apraxia, dystonia (ie, “fisted hand sign”), stimulus-sensitive myoclonus, parkinsonism unresponsive to dopaminergic therapy, and/or other lateralized cortical features (ie, corticobasal neglect, nonfluent aphasia, or visuospatial neglect). Although classically associated with CBD, the corticobasal syndrome is not specific for this disease. Its underlying pathology also includes Alzheimer’s disease, PSP, and tau or TDP-43 frontotemporal dementia.<sup>90,91</sup> As a result of the various clinical presentations and lack of specificity of the associated phenotypes, the clinical diagnosis of CBD remains extremely challenging. Efforts to develop standardized diagnostic criteria are underway. Other common CBD clinical phenotypes include primary progressive aphasia and frontotemporal dementia.

**Pathology.** Research efforts have led to the standardization and validation of neuropathological diagnostic criteria for CBD,<sup>92</sup> a necessary step for eventually validating clinical diagnostic criteria. CBD is characterized by deposits of 4-repeat tau in cortical and striatal neurons and glia, forming astrocytic plaques and thread-like lesions that affect white and gray matter. In view of the clinical and pathologic overlap between PSP and CBD, whether these are separate nosological entities is being questioned.<sup>93</sup> Despite overlap, both entities can be differentiated pathologically<sup>92</sup> and by protein sequencing and immunochemical analyses.<sup>94</sup> The CBD clinical phenotypes correspond to the topographical brain areas affected.

**Epidemiologic.** There are no epidemiologic studies on the incidence or prevalence of CBD, but clinicopathologic studies have shown that it is underdiagnosed<sup>91,95,96</sup> in view of its multiple phenotypes. CBD patients survive approximately 7–9 years, with shorter

survival in patients presenting with dementia than in those with corticobasal syndrome.<sup>97</sup>

**Genetic.** Like PSP, CBD is also associated with inheritance of an extended haplotype in the tau gene (H1 haplotype).<sup>78</sup> Moreover, there are FTDP-17 patients with defined tau mutations (eg, P-301, N279K) who may present with PSP or CBD phenotypes.<sup>98</sup>

**Pathogenic.** The major insight into the pathogenesis of CBD comes from the evaluation of the brains of patients with this disease. Hyperphosphorylated tau, inflammation, and oxidative injury are all proposed contributors to its pathogenesis.<sup>99,100</sup> It remains unclear what is the role of H1 in the risk for the disease; elevated levels of MAPT expression via increased transcription or alteration in splicing are rare.<sup>98</sup> What leads to the various phenotypic presentations and to the cascade of events involved in tau dysfunction and neurodegeneration remains to be understood.

**Therapeutic.** Therapeutic trials in CBD have not advanced significantly over the past 25 years. The major limitations include diagnostic difficulties and lack of validated outcome measures (ie, standardized rating scale).

### **Secondary Parkinsonism**

Secondary parkinsonism (SP) is the term used when referring to those cases of parkinsonism in which a specific cause is known. Whether PD associated with a known pathogenic mutation (“genetic PD”) is primary or secondary is a point of discussion, and the progress taking place in the field of the genetics of PD is reviewed elsewhere in this supplement of *Movement Disorders*.

In the last 25 years, remarkable progress has occurred in the field of SP. Progress has occurred in our understanding of known SPs such as Wilson disease, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), drug-induced or psychogenic parkinsonism through advances in the fields of molecular biology, diagnostic neuroimaging, and therapeutics, and we can now understand, diagnose, and offer better treatments to patients with these syndromes. Also, many new causes of parkinsonism have been identified in the last 2 decades such as parkinsonism induced by design drugs, paraneoplastic cases, HIV related, or induced by designer drugs such as cyclosporine or sodium valproate. Early recognition of SP is important because prompt medical intervention can in some cases reverse parkinsonism or greatly improve the medical outcome.

We summarize advances that have occurred in the field of SPs divided in sections, according to the etiology of the SP. Some SP are reviewed elsewhere in this

issue of *Movement Disorders*. (eg, psychogenic parkinsonism), and because of space limitation, other SPs will not be discussed here. Parkinsonism occurring as a manifestation of other genetically determined neurodegenerative disorders, for example, such as young-onset Huntington's disease, spinocerebellar degenerations, or frontotemporal dementia with parkinsonism, will also not be dealt with in this review, and the reader is referred to some reviews for additional information on the topic SP.<sup>101,102</sup>

### **Idiopathic Parkinsonism**

Approximately 15% of patients on long-term antipsychotic therapy develop drug-induced parkinsonism (DIP). Antidopaminergic drugs may unmask actual PD,<sup>103,104</sup> and underlying PD can be detected through dopamine transporter (DAT) imaging.<sup>104</sup> DIP may also be differentiated from PD by olfactory testing and cardiac scintigraphy.<sup>105,106</sup> Except for clozapine, all antipsychotics can induce parkinsonism, including the newer "atypical" ones. Other antidopaminergic drugs used for the treatment of gastrointestinal complaints, anxiety, or vertigo such as cinnarizine and sulpiride have been identified as a rather common cause of DIP.<sup>107</sup> Parkinsonism due to drugs that deplete presynaptic dopamine such as the antidyskinetic therapy tetraabenazene has also been recognized and may be amenable to treatment with L-dopa.<sup>108</sup>

### **Toxic Parkinsonism**

MPTP-induced parkinsonism was identified in 1983. In subsequent years the mechanism by which it damages the substantia nigra selectively was discovered, and this led to the development of several animal models of parkinsonism still currently in use. It also triggered an intense search for environmental causes of PD.<sup>109,110</sup>

Manganese-induced parkinsonism has regained prominence, mainly in Eastern Europe, as a hazard of methcathinone abuse. Methcathinone is a stimulant drug often manufactured in home laboratories using a process involving potassium permanganate, the source of the manganese poisoning.<sup>111,112</sup> Clinical findings and prognosis in these patients are typical of manganese-induced parkinsonism. Chronic low-level exposure to manganese from welding rods has recently been claimed to increase the risk of parkinsonism, but further research is needed before any definitive conclusions can be drawn.<sup>113</sup>

A number of industrial toxins have also been occasionally linked with parkinsonism. Carbon disulfide has been implicated recently in silo workers exposed to vapor.<sup>114</sup> Parkinsonism can also occur with mercury poisoning.<sup>115</sup> Cases of cyanide-induced parkinsonism have been reported.<sup>116,117</sup> A cluster of cases of PD and parkinsonism among coworkers in small

industrial plants manufacturing metal instruments where trichloroethylene (TCE) was used to degrease metal parts has been described. Chronic exposure to TCE can cause parkinsonism through mitochondrial complex 1 inhibition.<sup>118</sup>

### **Metabolic Disorders Causing Parkinsonism**

Progress about the cause, diagnosis, and treatment of Wilson disease (WD) has been important over the past 25 years. Mutations in *ATP7B*, a gene coding for a transmembrane copper-transporting ATPase on chromosome 13, have been identified in this autosomal recessive disorder.<sup>119</sup> Dozens of different mutations are known. WD is uniformly fatal if undetected and untreated. Treatment developments include the use of either tetrathiomolybdate or trientine in combination with lifelong copper chelation therapy and maintenance therapy with either zinc or trientine.<sup>120</sup> Stabilization of the clinical state is typical, and some WD patients experience significant reversal of disease manifestations.

Remarkable progress has also taken place in the last decade in the group of metabolic disorders associated with iron deposits in the brain—neurodegeneration with brain iron accumulation (NBIA)—which feature a movement disorder, intellectual decline, and a characteristic MRI appearance: low signal in the globus pallidus and often the substantia nigra on T2-weighted imaging (along with an isointense appearance on T1) consistent with iron deposition. NBIA include pantothenate kinase-associated neurodegeneration (PKAN; Hallervorden Spatz disease), neuroaxonal dystrophy, neuroferritinopathy, and aceruloplasminemia. New subtypes of NBIA have been identified such as fatty acid hydroxylase-associated neurodegeneration (FAHN), Kufor Rakeb syndrome (KRS), Woodhouse-Sakati Syndrome (WSS), and static encephalopathy with neurodegeneration in adulthood (SENDA).<sup>121</sup>

NBIAs can cause parkinsonism, frequently, but not always, mixed with dystonia, intellectual decline, and retinopathy. Responsible gene mutations have been found in these disorders except SENDA, and animal models have been developed for PKAN, NAD, NFT, FAHN, and WSS that will greatly facilitate efforts to develop rational therapies. Iron-chelating agents are being tested in PKAN, and testing of pantethine, which restores CoA levels, is also in the preclinical stage for these disorders.<sup>122–127</sup>

Parkinsonism may be the predominant manifestation<sup>128</sup> of acquired hepatocerebral degeneration. MRI discloses T1 hyperintensity in the putamen and globus pallidus. Clinical and radiologic similarities have implicated basal ganglia manganese deposition in the pathogenesis.<sup>129</sup> However, parkinsonism has also been attributed to hyperammonemia in chronic liver failure because of portal vein thrombosis.<sup>130</sup> Manganese intoxication has also been identified as the pathogenetic

mechanism for parkinsonism complicating total parenteral nutrition<sup>131</sup> and maintenance hemodialysis.<sup>132</sup>

Hereditary hemochromatosis is a known cause of hepatocerebral degeneration. However, recent cases of parkinsonism in patients with hemochromatosis have shown T2 MRI basal ganglia hypointensities, more consistent with abnormal levels of iron accumulation.<sup>133</sup>

Parkinsonism together with dystonia is a prominent clinical feature of rapid-onset dystonia parkinsonism. This rare syndrome is produced by missense mutations in the *ATP1A3* gene.<sup>134</sup> A growing number of mitochondrial respiratory chain disorders have been associated with parkinsonism.<sup>135–139</sup>

### **Infection-Related Parkinsonism**

The most common infectious disease setting for parkinsonism currently is human immunodeficiency virus (HIV) infection. HIV can cause Parkinson's syndrome, either as a result of direct viral damage in HIV encephalopathy<sup>140</sup> or through an opportunistic infection (eg, toxoplasma or cryptococcal abscess in the basal ganglia).<sup>141,142</sup> In a recent series of more than 2000 HIV-positive cases from South America, 28 had movement disorders, and 14 of these had parkinsonism. In 12, direct HIV infection involving the nigra was believed to be responsible.<sup>143</sup> The incidence of HIV-encephalopathy parkinsonism may have declined since the advent of antiretroviral therapy,<sup>144</sup> which can produce remissions in already-affected individuals.<sup>145</sup> However, it has been argued that HIV infection and retroviral therapy accelerate the aging process and lead to earlier onset of degenerative diseases such as PD.<sup>146</sup>

### **Paraneoplastic Hypokinetic Syndromes**

Paraneoplastic causes of parkinsonism can occur with any paraneoplastic encephalomyelitis, but are rare.<sup>147</sup> Vertical gaze paresis is common (60%), sometimes with complete external ophthalmoplegia. Some patients have a catatonic-like presentation, with hypokinesia, severe rigidity, or waxy flexibility.<sup>148–150</sup> This syndromes commonly arises after a viral-like prodrome of headache, fever, and anxiety and may be followed by autonomic instability, hypoventilation, and hyperthermia, associated with muscle rigidity, facial grimacing, abdominal contractions, and intermittent dystonia. Cases resembling parkinsonism or multisystem atrophy have been reported with lung carcinoma.

The pathogenesis of hypokinetic forms of basal ganglia is similar to other encephalomyelitic presentations with emphasis on degeneration of the basal ganglia. The clues toward a paraneoplastic etiology are the subacute presentation and rapidly progressive course over weeks/months and inflammatory CSF. Paraneoplastic autoantibody evaluation may, if positive, confirm the cause and point toward the site of the primary tumor. Hypokinetic presentations can often

be the presenting feature in patients with anti-Ma2-associated encephalitis. Where anti-Ma-2 is present in young males, a testicular tumor should be sought.<sup>147</sup>

### **Vascular Parkinsonism**

Studies by Fitzgerald and Jankovic (1989)<sup>151</sup> renewed interest in the important topic of vascular parkinsonism (VP). They emphasized classical "lower-half" Parkinson's syndrome, which is frequently associated with confluent subcortical white matter ischemia and lacunar infarcts. Clinically, most reviews and studies have considered VP based on 2 principle settings: one characterized by a bilateral akineto-rigid syndrome dominated by gait disturbances (lower-body parkinsonism) associated with multiple and diffuse subcortical and periventricular white matter lesions affecting thalamocortical drive and another, less common type of acute or subacute onset featuring parkinsonian signs contralateral to strategic infarcts of the striatum, affecting putaminopallido-thalamic loops. DAT SPECT imaging is usually normal in patients with VP associated with subcortical small vessel disease and has been used to differentiate this form of parkinsonism from idiopathic PD at a group level.<sup>152</sup>

A detailed clinicopathological investigation of 17 highly selected patients presenting with parkinsonism for which no alternative pathological cause could be found compared with aged matched controls with comparable vascular risk factors generated operational criteria for the clinical diagnosis of VP.<sup>153</sup> The use of the University of Pennsylvania Smell Test may also be a helpful discriminator, as olfaction appears to be preserved in VP, whereas 80% of patients with Parkinson's disease are hyposmic.<sup>154</sup>

Rare cases of Parkinson's syndrome have also been reported in association with systemic lupus erythematosus, causing cerebral vasculitis, which is variably responsive to corticosteroids and immunosuppressive agents, antiphospholipid syndrome, and Moya-Moya disease.<sup>155</sup>

## **Conclusions**

During the last decades atypical and secondary parkinsonian disorders have been increasingly recognized as important causes of parkinsonism. Although treatment options are still limited, remarkable progress has been achieved through advances in the genetics, molecular biology, and neuroimaging of these disorders. Early diagnosis has become more important because trials of disease-modifying therapies are beginning to enter the clinic. During the next decade we will see an even more intense search for genomic, proteomic, and neuroimaging derived biomarkers, particularly in atypical parkinsonian disorders. In addition, the search for novel interventional therapies targeting key pathogenic events will accelerate.

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