Parkinsonism Plus Syndromes

9

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Abstract Parkinson's plus syndrome is a term that refers to disorders of movement and cognition that are often confused with Parkinson's disease. The three main disorders are progressive supranuclear palsy (PSP), multisystem atrophy (MSA), and corticobasal degeneration (CBD). These syndromes are pathologically diverse encompassing a number of distinct proteinopathies but have in common clinical features of movement abnormality, cognitive decline, a more rapid clinical course than Parkinson's disease, and a generally poor therapeutic response to levodopa. The diagnosis is largely clinical with some reliable radiological features. Therapy is largely in the realm of multidisciplinary symptomatic support but advances in molecular and biological understanding is leading to exciting therapeutic avenues.

Keywords Corticobasal degeneration • Mid brain atrophy • Mulitsystem atropy • Parkinson's plus • Pontocerebellar atrophy • Shy-Drager syndrome • Supranuclear palsy

Introduction

The three main parkinsonism plus disorders are progressive supranuclear palsy (PSP), multiple system atrophy (MSA), and corticobasal degeneration (CBD). These are neurodegenerative disorders that are frequently confused with idiopathic Parkinson's disease (PD). In fact, about 30% of pathologically proven parkinsonism plus syndromes are initially misdiagnosed as PD. Other causes of parkinsonism, other than PD and the parkinsonism plus disorders, include secondary parkinsonism and hereditary neurodegenerative disorders, but these are outside the scope of this chapter (Table 9.1).

Accurate differentiation between parkinsonism plus syndromes and PD is important for several reasons, the two most significant being:

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O. Hardiman and C.P. Doherty (eds.), *Neurodegenerative Disorders*,
DOI: 10.1007/978-1-84996-011-3_9,

Table 9.1 Classification of parkinsonism: a subdivision of parkinsonism according to known etiology

Idiopathic Parkinson's disease	• Parkinson's disease • Genetic forms of Parkinson's Disease
Parkinsonism plus syndromes	• Progressive supranuclear palsy • Multiple system atrophy • Cortico-basal ganglionic degeneration • Parkinsonism-dementia complex
Hereditory neurodegenerative parkinsonism	• Huntington's disease • Wilson' disease • Autosomal dominant spinocerebellar ataxias • Lubag (X-linked dystonia-parkinsonism) • Neuroacanthocytosis • Familial basal ganglia calcification • Frontotemporal dementia with parkinsonism • Brain iron accumulation disorders • Pallidopyramidal syndromes (usually genetic)
Secondary (acquired, symptomatic) parkinsonism	• Infectious: postencephalitic, AIDS, SSPE, Creuzfeldt−Jakob disease • Drugs: dopamine receptor blocking drugs; reserpine, lithium, flunarizine, valproate • Toxins: MPTP, CO, Mn, Hg, cyanide, methanol, ethanol • Vascular: multi-infarct • Trauma: pugilistic encephalopathy • Other: parathyroid abnormalities hypothyroidism, hepatocerebral degeneration, brain tumor, paraneoplastic, normal pressure hydrocephalus

- Life expectancy is much lower in parkinsonism plus.
- Treatments such as levodopa and deep brain stimulation are generally ineffective in parkinsonism plus.

A complete history and neurological examination is critical in establishing a correct diagnosis. Atypical features such as eye movement disorders, early falls, and early cognitive impairment should raise suspicion of a parkinsonism plus syndrome, and all patients with suspected PD should have regular reviews and examinations. Table 9.2 provides a guide to some clinical red flags that should make the examiner consider an alternative diagnosis to PD.

Multiple System Atrophy

Clinical Features

Like PSP and CBD, MSA is a progressive, sporadic, adult-onset neurodegenerative disorder. The first cases were described over a 100 years ago by Dejerine and Thomas who referred to olivopontocerebellar atrophy. The term MSA was introduced in 1969 by

Table 9.2 Red flag features in parkinsonism. A list of red flag clinical markers, which may help the clinician differentiate parkinsonism plus disorders at the bedside

Clinical feature	Likely cause of parkinsonism
Young onset	Juvenile PD, MSA
Axial rigidity	PSP
Pill rolling rest tremor	PD
Myoclonus	MSA, CBD
Vertical gaze palsy	PSP
Early falls backward (1st year)	*PSP*
Asymmetric onset	*PD, CBD*
Alien limb/apraxia	*CBD*
Poor response to levodopa	*PSP, CBD, MSA*
Dysautonomia	*MSA*
Early cognitive impairment	*PSP, CBD*
Laryngeal stridor	*MSA*
Palilalia	PD, PSP
Cerebellar signs	*MSA*
Pyramidal signs	*MSA*

Graham and Oppenheimer indicating that multiple brain systems are involved (extrapyramidal, pyramidal, cerebellar, and autonomic [in any combination]). Patients are clinically classified according to the predominant motor presentation, for example, cerebellar (MSA-C) and parkinsonian (MSA-P) subtype. When autonomic failure predominates or there is primary autonomic failure, MSA is sometimes termed Shy-Drager syndrome, although this term is rarely used nowadays.

Table 9.3 shows an international bedside classification system for MSA according to differing levels of diagnostic certainty: possible, probable, or definite. Autonomic dysfunction is usually the earliest feature in both MSA-P and MSA-C, with 97% ultimately developing symptoms. Genitourinary dysfunction is the most frequent initial complaint in women, and early erectile dysfunction is invariable in men. Orthostatic hypotension is common and is present in at least 68% of patients. Symptoms associated with orthostatic hypotension include light headedness, dizziness, blurred vision, fatigue, yawning, and syncope. Akinesia and rigidity are prominent in MSA-P but are usually also evident in the later stages of MSA-C. Cerebellar dysfunction is predominant in MSA-C with gait and limb ataxia the prominent features. Notable features supporting a diagnosis of MSA include rapid progression (wheelchair bound <10 years from onset), orofacial dystonia, camptocormia (forward trunk flexion), Pisa syndrome (lateral trunk flexion), disproportionate antecollis (severe neck flexion), dysphonia (hoarse/harsh/high pitched), dysarthria, dysphagia, inspiratory stridor (involuntary deep sighs), cold hands and feet, emotional incontinence, pyramidal signs (Babinski and hyperreflexia), and a jerky myoclonic postural/action tremor. A pill-rolling or rest tremor should suggest PD. Only one-third of patients with MSA-P respond to levodopa and about 90% are unresponsive to long-term therapy.

MSA progresses rapidly and most patients develop motor impairment within 1 year of onset. Motor impairment can be caused by cerebellar dysfunction, and corticospinal tract

Table 9.3 Criteria for diagnosis of MSA

Definite MSA Neuropathological findings of widespread and abundant CNS alpha-synuclein-positive glial cytoplasmic inclusions with neurodengenerative changes in striatonigral or olivopontocerebellar structures
Probable MSA A sporadic progressive, adult (>30 y)-onset disease characterized by • Autonomic failure involving urinary incontinence or an orthostatic decrease of blood pressure within 3 min of standing by at least 30 mmHg systolic or 15 mmHg diastolic and • Poor levodopa-responsive parkinsonism or • A cerebellar syndrome/dysfunction
Possible MSA • Parkinsonism or • A cerebellar syndrome/dysfunction and • At least one feature suggesting autonomic dysfunction (otherwise unexplained urinary urgency, frequency, or incomplete bladder emptying, erectile dysfunction or significant orthostatic blood pressure that does not meet the level required in probable MSA) • At least one of the additional features shown in Table 9.4

Modified from the second consensus statement on the diagnosis of multiple system atrophy – Gilman et al. 2008

Table 9.4 Additional features of possible MSA

Possible MSA-P or MSA-C • Pyramidal signs – Babinski sign with increased tendon reflexes • Stridor
Possible MSA-P • Rapidly progressive parkinsonism • Poor response to levodopa • Postural instability within 3 years of motor onset • Gait ataxia, cerebellar dysarthria, limb ataxia, or cerebellar oculomotor dysfunction • Dysphagia within 5 years of motor onset • Atrophy on MRI of putamen, middle cerebellar peduncle, pons, or cerebellum • Hypometabolism on FDG-PET in putamen, brainstem, or cerebellum
Possible MSA-C • Parkinsonism • Atrophy on MRI of putamen, middle cerebellar peduncle, or pons • Hypometabolism on FDG-PET in putamen • Presynaptic nigrostriatal dopaminergic denervation on SPECT or PET

MSA multiple system atrophy, *MSP-P* MSA with predominant parkinsonism, *MSA-C* MSA with predominant cerebellar ataxia, *FDG* (18) fluorodeoxyglucose

dysfunction can also occur but is not a major symptomatic feature of the condition. At least 50% of all patients with probable MSA are disabled or wheelchair-bound within 5 years after onset and the median survival is 9.5 years.

Epidemiology

There is an estimated incidence of 1.2–4.1 cases/100,000 population/year, with an estimated prevalence of 0.9–8.4 cases/100,000. However, like PSP and CBD, this is probably underestimated, as misdiagnosis is not uncommon. About 30% of patients with late-onset sporadic cerebellar ataxia have MSA. MSA has been reported in Caucasian, African, and Asian populations. MSA-P predominates in western countries (68–82%), and in eastern countries, MSA-C is common with 67% of patients. There is a male predominance (2:1), and the mean patient age at onset is 54.3 years with a range of 33–78 years.

Neuropathology and Molecular Pathology

The neuropathology of MSA-C is olivopontocerebellar degeneration (inferior olivary nucleus, pons, and cerebellum) and MSA-P is striatonigral degeneration (substantia nigra, putamen, caudate nucleus, and globus pallidus). Even though they can be clinically very different, MSA-C and MSA-P share oligodendroglial cytoplasmic inclusions (GCIs) as a unifying pathological feature (Fig. 9.1). Both subtypes display neural loss and gliosis in their respective regional brain distribution and both are frequently accompanied by neurodegeneration of the autonomic nervous system; the severe clinical correlate of this is Shy-Drager syndrome.

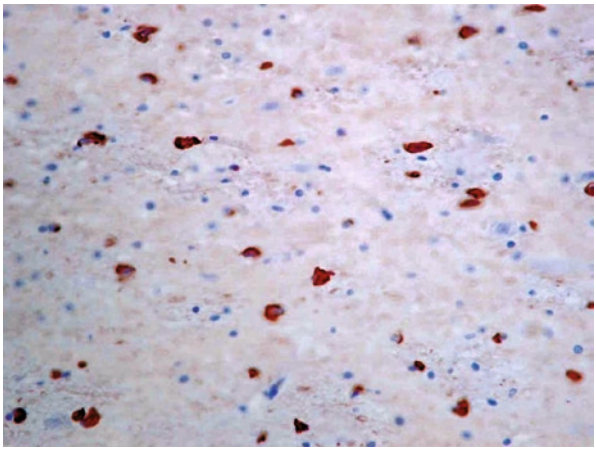

Fig. 9.1 Alpha-synuclein immunostaining to show cytoplasmic immunopositivity in glial cells (glial cytoplasmic inclusions [*GCI*]) within subcortical white matter (magnified ×40 before photo enlargement) (Photo courtesy Professor Michael Farrell)

Table 9.5 Neurodegenerative disorders classified on whether microtubule-associated tau or alpha-synuclein is the primary protein aggregate

Synucleinopathies	Tauopathies
Progressive supranuclear palsy	Parkinson's disease
Frontotemporal dementia	Multiple system atrophy
Corticobasal disease	Lewy body dementia
Pick's disease	
Argyrophilic brain disease	
PD—dementia complex—Guam	
Post-encephalitic PD	

Approximately 30% of Caucasian patients have principally striatonigral pathology, 20% olivopontocerebellar pathology, and the remaining 50% have equal amounts of both. Pathological degeneration of the putamen appears to correlate with the poor levodopa response in MSA.

Oligodendroglial cytoplasmic inclusions, which define MSA neuropathology, are formed by fibrillized alpha-synuclein protein. Genome studies have found genetic association between common single nucleotide polymorphisms (SNPs) in the alpha-synuclein gene and MSA risk and transgenic mice over-expressing alpha-synuclein develop oligodendroglial cytoplasmic inclusions. This makes MSA a "synucleinopathy" similar to PD and dementia with Lewy Bodies (see Table 9.5).

Aberrant myelin basic protein may also be pathogenic in MSA, raising the possibility that this is a primary disorder of myelin-producing oligodendroglial cells. However, no studies to date have linked these two plausible hypotheses.

Laboratory Tests

Investigations of autonomic function include the table-tilt test to measure orthostatic blood pressure and sphincter electromyography. The latter detects denervation in the external urethral sphincter secondary to degeneration of Onuf's nucleus in the spinal cord. Cardiac scintigraphy demonstrates reduced sympathetic MIBG uptake in the heart in PD but not MSA. Clinically, this test is more commonly used in Eastern countries than in the West.

Radiological Findings

Magnetic resonance image (MRI) findings in MSA-P often show decreased signal bilaterally in the posterolateral putamen on T2-weighted images. In addition, to putaminal hypointensity on T2, a characteristic finding in MSA is the slit-hyperintensity in the lateral margin of the putamen. The MRI abnormalities of MSA-C consist of atrophy of the pons, middle cerebellar peduncles, and cerebellum. A characteristic "hot cross bun sign" is produced by selective loss of myelinated transverse pontocerebellar fibers and neurons in the pontine raphe with relative preservation of the pontine tegmentum and corticospinal tracts.

Management

There is no effective drug therapy and a multidisciplinary approach is recommended. Orthostatic hypotension is often the earliest and most debilitating symptom. The addition of liberal salt, increasing fluid intake, head elevation when sleeping, and elastic stockings may improve standing blood pressures. It is worth considering levodopa replacement but the results are usually poor. Several drugs are used for the management of orthostatic hypotension, including fludrocortisone (mineralocorticoid), midodrine (alpha1-adrenoreceptor agonist), droxidopa (synthetic precursor of norepinephrine), and nonsteroidal anti-inflammatory drugs (NSAIDs) (possible inhibition of vasodilator prostaglandins). Therapy can be limited by supine hypertension, which affects up to 60% of patients. Bladder symptoms including urinary retention and incontinence are relatively common and troublesome problems. Formal urodynamics with measurement of post-micturition volumes are important. Overactive bladder symptoms may improve with anti-muscarinics such as oxybutynin or tolterodine while some patients require intermittent self-catheterization. Medication may also be considered for constipation and erectile dysfunction.

Progressive Supranuclear Palsy

Clinical Features

Steele, Richardson, and Olszewski presented the first clinicopathological descriptions of PSP in 1963 and 1965. Unsteadiness of gait and falls within the first year, frequently backward, is the presenting feature in more than 60% of cases. Bradykinesia and rigidity may be associated, often resulting in a misdiagnosis of PD. In a minority of cases, gaze palsy, dysarthria, or dysphagia may be the prominent early symptoms. The illness progresses to an immobile state over less than 10 years in the majority of cases.

In contrast to the short and shuffling gait, stooped posture, narrow base, and flexed knees typically seen in PD, the PSP patients tend to be erect with a stiff and broad-based gait with a frontal recklessness. They tend to pivot when turning, which further compromises balance. The speech is dysarthric rather than hypophonic and there is no rest tremor. Some PSP patients may present with a syndrome of pure akinesia manifest by freezing and gait initiation failure, marked impairment of speech (stuttering, stammering, hypophonia) and micrographia, eyelid motor disturbance (blepharospasm, eyelid apraxia) without significant rigidity or tremor or dementia, and without response to levodopa. Although the PSP gait can appear ataxic, cerebellar signs are not a feature.

Oculomotor abnormalities are common in PSP. Symptomatic eye movement difficulty is typically present within 4 years after the onset. Prior to this, most patients have slowing of vertical saccades, saccadic pursuit, break down of opticokinetic nystagmus in the vertical plane, poor convergence, and square-wave jerks (SWJs). The latter occurs in nearly all patients with PSP and rarely in PD. Vertical supranuclear ophthalmoparesis is a prominent feature of PSP. The patient loses range of vertical gaze, with downgaze usually worse than upgaze. This gaze restriction can be overcome by using the vestibulo-ocular reflex (Dolls

eye manoeuver) achieved by passive flexion/extension of the neck. Involuntary orbicularis oculi contractions producing blepharospasm and "apraxia" of eyelid opening and eyelid closure affect up to one-third of PSP patients.

Pseudobulbar symptoms in PSP patients are characterized by dysarthria, dysphagia, and emotional lability. The classic speech is a low-pitched dysarthria. Some patients have severe stuttering and palilalia.

Cognitive impairment is a prominent feature of PSP, often presenting as cognitive slowing, impairment of executive functions, and with a subcortical dementia picture. Apathy and hypoactive behaviors have been attributed to a dysfunction in the frontal cortex and associated circuitry. Sleep problems are common and often correlate with worsening dementia.

In addition to the classical presentation of PSP, there is a more benign form known as PSP-P, with clinical similarity to PD, good response to levodopa, and delayed onset or absence of supranuclear palsy. Pathologically, these phenotypes are characterized by differences in the isoform composition of insoluble tangle-tau isolated from the brainstem.

Relative sparing of olfaction helps to differentiate PSP from PD and MSA.

Death, often by aspiration, usually occurs within 10 years of onset with a mean survival of about 6 years.

Epidemiology

There is an estimated incidence of 0.3–1.1 cases/100,000 population/year, with an estimated prevalence of 6.2–7.4 cases/100,000. No racial predilection is known. Men are more commonly affected and the mean age of onset is 63 years.

Neuropathology and Molecular Pathology

PSP shares histological and molecular similarities with other "tauopathies" such as Alzheimer's disease, frontotemporal dementia, and argyrophilic grains disease (Table 9.5). Tau is a microtubule-associated protein, meaning that it regulates the structure and stability of a major axon protein trafficking system. When tau protein is hyperphosphorylated, it tends to form aggregates/inclusions. These are termed neurofibrillary tangles when occurring in glial cells, coiled bodies in oligodendrocytes, and "tufted" inclusions in astrocytes (Fig. 9.2). The neurofibrillary tangles in PSP are single straight filaments and are common in subcortical regions whereas in Alzheimer's disease, they are paired helical filaments and cortical.

Alternative exon splicing of the tau gene produces six isoforms in human brain. Isoforms containing exon 10 have four microtubule-binding domains (4R tau) and those that splice out exon 10 have three (3R tau). In the normal brain, 3R and 4R tau isoforms have similar ratios; in PSP and CBD there is a 4R preponderance, and in Pick's disease a 3R preponderance. Certain tau gene mutations, including some that disrupt the stem loop structure that splices exon 10, cause an autosomal dominant frontotemporal dementia with parkinsonism (FTDP-17) supporting the key role of the tau gene in tauopathy-associated neurodegeneration (see Chap. 6).

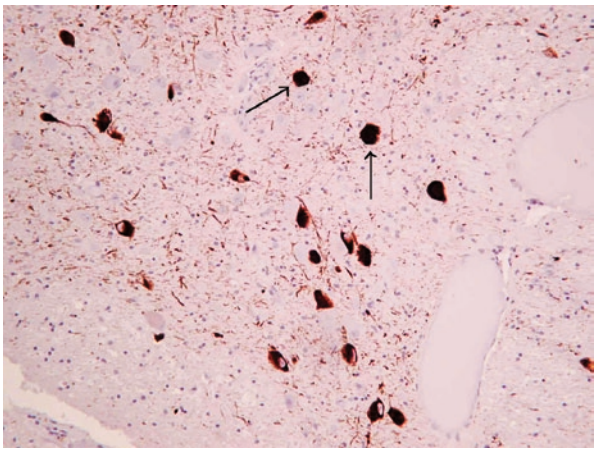

Fig. 9.2 Tau immunostaining to show neuronal cytoplasmic tau-positive neurofibrillary tangles (*arrows*). (Photo courtesy Professor Ian R.A. Mackenzie)

Certain tau mutation carriers with FTDP-17 have a phenotype similar to PSP but tau mutations do not cause PSP and in clinical practice familial clustering of PSP is very rare. However, one of the most compelling and robust associations between gene and phenotype across all known human disorders is the association between sporadic PSP and a specific H1 haplotype formed by a balanced inversion of the region surrounding the tau gene about three million years ago. A number of polymorphisms on the H1 haplotype that influence gene expression have been implicated. Genetic testing of the tau gene is unnecessary in PSP unless one is considering an alternative differential diagnosis such as autosomal dominant FTDP-17.

Radiological Findings

Generalized brain atrophy is common in PSP, especially in the frontal lobes, but the characteristic finding of dorsal midbrain atrophy is best seen on a dedicated axial MRI where it produces a picture reminicent of "Mickey Mouse" (Fig. 9.3), and on sagittal views where it produces a picture similar to a hummingbird (Fig. 9.4).

Laboratory Tests

There are no diagnostic tests currently available for PSP; the diagnosis remains a clinical one (Table 9.6).

Management

There is no effective treatment for PSP and therapy is generally supportive in nature. A multidisciplinary team approach is recommended; physiotherapists may improve mobility, prevent contractures, and provide hip protectors and walking aids; occupational therapists

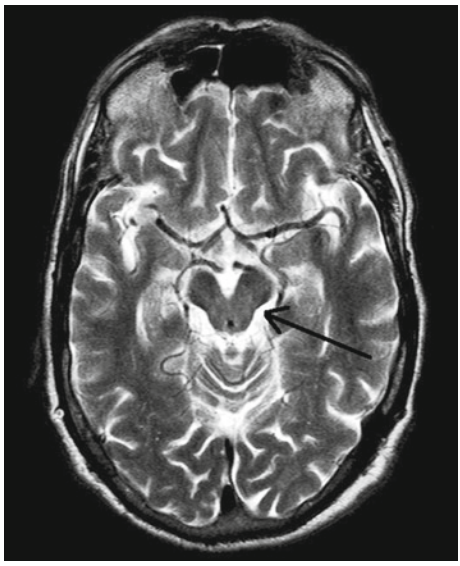

Fig. 9.3 Axial T2-MRI showing voulme loss in midbrain giving "Mickey Mouse" appearance (*arrow*) in PSP

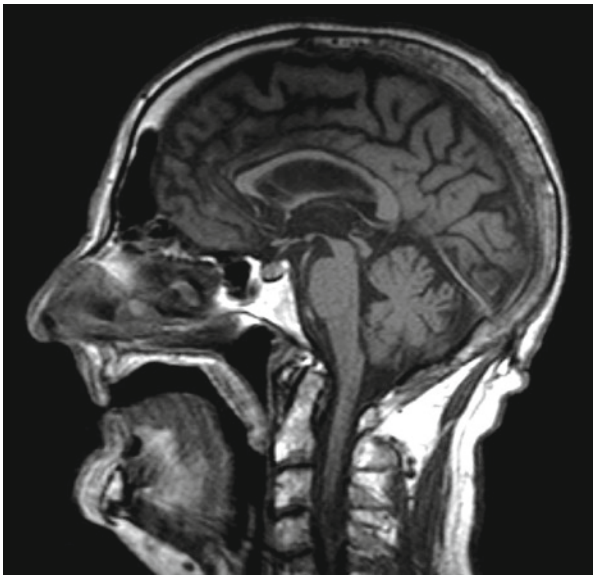

Fig. 9.4 Sagittal T1-MRI through the brainstem showing volume loss in the midbrain with relative preservation of the pons in PSP. The upper convexity of the midbrain is lost giving a "hummingbird" appearance

and social workers can assist with adapting patients' homes. Speech and language therapists may provide communication devices if required.

If parkinsonism is a prominent feature, a trial of levodopa is recommended, increasing the dose to at least 1 g/day before deciding it is of no benefit. Forty to fifty percent show some improvement although this is often short lived. Adverse effects include visual hallucinations and rarely dystonia, dyskinesias, and apraxia of eyelid opening. Amantidine may benefit 15% of patients but the response is usually modest. Dopamine agonists,

Table 9.6 Clinical research criteria for the diagnosis of PSP.

Possible PSP • Gradually progressive disorder • Onset age ≥ 40 or later • Vertical (upward or downward gaze) supranuclear palsy[a] *or* slowing of vertical saccades[a] and prominent postural instability with falls in the first year of disease onset[a] • No evidence of other disease that could explain the foregoing features, as indicated by mandatory exclusion criteria
Probable PSP • Gradually progressive disorder • Onset age ≥ 40 or later • Vertical (upward or downward gaze) supranuclear palsy[a] and prominent postural instability with falls in the first year of disease onset • No evidence of other disease that could explain the foregoing features, as indicated by mandatory exclusion criteria
Definite PSP • Clinically probable or possible PSP and histopathologic evidence of typical PSP[b]
Mandatory exclusion criteria • Recent history of encephalitis • Alien limb syndrome, cortical sensory deficits, focal frontal or temporoparietal atrophy • Hallucinations or delusions unrelated to dopaminergic therapy • Cortical dementia of Alzheimer's type • Prominent, early cerebellar symptoms or prominent, early unexplained dysautonomia (marked hypotension and urinary disturbances) [a] • Severe, asymmetric parkinsonian signs • Neuroradiologic evidence of a relevant structural abnormality (i.e., basal ganglia or brainstem infarct, lobar atrophy) • Whipple's disease, confirmed by polymerase chain reaction, if clinically indicated
Supportive criteria • Symmetric akinesia or rigidity, proximal more than distal • Abnormal, neck posture, especially retrocollis • Poor or absent response of parkinsonism to levodopa therapy • Early dysphagia and dysarthia • Early onset of cognitive impairment including at least two of the following: apathy, impairment in abstract thought, decreased verbal fluency, imitation behavior, and frontal release signs

Based on the report of the NINDS-SPSP international workshop. Litvan et al., Neurology. 1996;47:1–9

This provides a useful clinical and research guide to the diagnosis of definite (pathology), probable, and possible PSP

[a]Upward gaze is considered abnormal when pursuit or voluntary gaze, or both, have a restriction of at least 50% of the normal range

[b]Definite PSP is a clinicopathologic diagnosis

monoamine oxidase inhibitors, and catechol-O-methyl transferase inhibitors are of no proven benefit. Anticholinergics should be avoided as there is an unusual sensitivity to cholinergic blockade in these patients. Lorazepam and low-dose quetiapine could be considered for management of psychiatric and behavioral symptoms.

Blepharospasm, with or without eyelid freezing, can be effectively treated with botulinum toxin. Dysphagia is progressive and some patients choose percutaneous endoscopic gastrostomy (PEG) insertion.

Corticobasal Degeneration

Clinical Features

CBD was first described by Rebeiz et al. in 1968 in three patients of Irish descent with parkinsonism, myoclonus, supranuclear palsy, and apraxia who were found at autopsy to have "corticodentatonigral degeneration with neuronal achromasia." This disorder has an insidious onset with progressive asymmetric rigidity and apraxia. Severe disability and death typically occurs within 10 years. Definite diagnosis requires histological examination.

Cortical dysfunction may manifest as asymmetric ideomotor apraxia (disorder of skilled, learned, purposeful movement) and/or an alien limb ("My hand has a mind of its own"). Eye movement abnormalities with slow initiation of horizontal movements as well as upgaze are common. However, restricted downgaze is suggestive of PSP. In a series of 147 cases collected from eight centers, the following features were most common: parkinsonism, (100%), higher cortical dysfunction (93%), dyspraxia (82%), gait disorder (80%), dystonia (71%), tremor (55%), myoclonus (55%), alien limb (42%), cortical sensory loss (33%), dementia (22%). Asymmetrical limb contractures are more prevalent in this condition than in the other parkinsonism plus syndromes. The motor alien hand must be differentiated from sensory or posterior syndrome associated with a lesion in the thalamus and temporal-occipital lobe. In autopsy-proven cases of CBD, the following were found to be the best predictors of the diagnosis of CBD: limb dystonia, ideomotor apraxia, myoclonus, and asymmetric akinetic-rigid syndrome with late onset of gait or balance disturbance.

Epidemiology

There is an estimated incidence of 0.02–0.92 cases/100,000 population/year, with an estimated prevalence of 4.9–7.3/100,000. No racial predilection is known. The condition tends to occur in older age groups (60–80 years), with a mean age of onset of 63 years. CBD may be more common in women.

Radiological Findings

MRI brain findings are nonspecific but often show asymmetric posterior parietal and frontal cortical atrophy. Atrophy of the corpus callosum has also been described.

Neuropathology and Molecular Pathology

CBD is another tauopathy with similar molecular characteristics to PSP, differing mainly in regional brain pathology. Rebeiz described CBG in 1968 as "corticodentatonigral degeneration with neuronal achromasia"; patients with prominent frontoparietal degeneration get limb apraxia and dementia and those with prominent frontotemporal atrophy get progressive primary aphasia. Severe substantia nigra depigmentation is invariable and most patients have some extrapyramidal features/parkinsonism.

CBD and PSP are both 4R tauopathies and the tau H1 haplotype is a shared risk factor. Almost half of all CBD patients are misdiagnosed PSP in life and 30% of CBD turns out to be PSP at postmortem. However, CBD and PSP are not different spectrums of the same disorder since their classical clinical presentations can be strikingly different and the neuropathological diagnostic criteria of CBD and PSP are validated with high sensitivity and specificity. Both share neuronal tau accumulation but astrocytic plaques are the hallmark of CBD and tufted astrocytes the hallmark PSP. Prominent cortical and subcortical neuronal loss, often highly asymmetric, also separates CBD from PSP. Ballooned swollen neurons with loss of cytoplasmic staining (achromasia), is supportive when present in the cortex and basal ganglia.

Management

To date, no effective treatment has been found. Initially, the extrapyramidal symptoms including rigidity, bradykinesia, and tremor may respond to levadopa. Clonazepam and levetiracetam can be tried for myoclonus. Painful rigidity and dystonia may improve with botulinum toxin injections. Physical and occupational therapy can be helpful in patients with impaired gait secondary to visual agnosia.

Other Environmental Tauopathies

Clusters of PSP-like disorders exist in a number of remote parts of the world. In Guadeloupe, a PSP-like presentation of parkinsonism is as common as idiopathic PD. The consumption of soursop, which contains high concentrations of annonacin, has been suggested as annonacin can cause direct inhibition of Complex 1. Interestingly, association between Guadeloupian parkinsonian and the H1 tau haplotype has been reported, as has 4R tau pathology at postmortem.

A parkinsonism–dementia complex sometimes with features of motor neuron disease is another tauopathy described amongst the Chamorro population of Guam and isolated villages on the Kii peninsula of Japan. The incidence of this disorder has declined since the original 1945 description by Zimmerman. Flour made from the false sago palm (*Cycas micronesica*) has been implicated as it contains high levels of an excitatory amino acid BMAA, but this theory remains completely unproven. Familial clustering is described as is weak genetic association with the tau gene.

Encephalitis lethargica (EL) is characterized by somnolence, sleep inversion, oculogyric crises, and behavioral disorders. Most cases of EL occurred during the 1918/19 influenza pandemic and an etiological association has been suggested but not proven. Many patients who recovered from the somnolent phase developed partial dopa responsive parkinsonism sometimes years after the acute disease. Sporadic cases still occur rarely. Pathologically, EL shows subcortical and brainstem neurofibrillary pathology comprised of both 3R and 4R tau.

Hereditary Mimics

A number of single gene disorders can occasionally mimic the atypical parkinsonisms. Progranulin mutation carriers, who lack tau neuropathology, typically present with a frontal lobe behavior and language disturbance but can resemble PSP and CBD. LRRK2 mutation carriers typically display PD and Lewy body neuropathology, but in some kindreds, primary tau pathology resembling PSP occurs for unknown reasons. The fragile X tremor-ataxia syndrome (FXTAS) and a number of the autosomal dominant spinocerebellar ataxias (SCA) clinically mimic MSA-C.

Biomarkers in PSP, MSA, and CBD

Presently, there are no fully reliable markers for PSP, MSA, or CBD although, as discussed, standard MRI often shows characteristic features in PSP (mid brain atrophy [humming bird sign]), MSA (pontocerebellar atrophy [hot cross bun and lateral putaminal sclerosis]), and CBD (frequent asymmetrical parietal lobe atrophy).

Phosphorylated tau protein has been examined in the CSF as a potential biomarker for PSP but results are inconsistent and confounded by elevated tau protein in overlapping neurodegenerative disorders like Alzheimer's disease.

Functional evaluation of the presynaptic dopaminergic system using dopamine transporter single photon emission computed tomography (SPECT) scanning is widely available in clinical practice does not reliably differentiate PD, PSP or MSA and, therefore, is of little value. Studies of dopamine D2 receptors SPECT have shown normal or upregulation in PD whereas, typically, this is reduced in MSA and PSP.

A better modality is fluorodeooxyglucose positron emission tomography (FDG-PET) although this is not widely available. Recent computer programs for FDG-PET that recognize disease-specific patterns show remarkable accuracy in differentiating parkinsonisms even before examined by a clinician. In PD, the pattern is increased pallidothalamic and pontocerebellar metabolic activity and reduced activity in premotor cortex, supplementary motor area, and parietal association regions. MSA is characterized by bilateral metabolic reductions in putamen and cerebellar activity, and PSP by reductions in the upper brainstem, medial frontal cortex, and medial thalamus.

FDG-PET is most specific in the early phase of disease when the clinical diagnosis is hardest and accords with the time window where disease-modifying treatments might be most effective. Functional imaging of the cholinergic system and of activated microglia hold promises for the future. Imaging technologies that directly indentify intraneuronal inclusions such as NFTs and Lewy bodies are likely in the future.

Rapid eye movement (REM) sleep behavior disturbance (RBD) is common to synucleinopathies (PD, MSA) and rare in tauopathies (PSP, CBD) and invariably precedes the movement disorder. The vast majority of patients diagnosed with RBD go on to develop PD or MSA, marking RBD a clinically useful biomarker and identifying a target patient group for future disease-modifying therapies. Neuropsychological tests (e.g., Frontal Assessment Battery) may show disproportionately early frontal pathology, apathy, and/or executive dysfunction and differentiate PSP from PD and other atypical parkinsonisms. The simple 3-clap applause test is a very sensitive bedside test with perseveration, pointing to PSP.

Future Advances

Drugs that inhibit alpha-synuclein aggregation have been an area of active investigation in MSA and PD. The antibiotic rifampicin inhibits alpha-synuclein aggregation in transgenic mouse models of MSA. An important rodent study showed that embryonic striatal graft transplantation restored L-dopa responsiveness, which if applied to humans might be analogous to turning the parkinsonism of MSA into that of PD.

The NNIPPS study is the only large placebo-controlled double-blind trial in PSP (362 patients) or MSA (398 patients), and this failed to show any benefit from the anti-excitotoxin drug riluzole.

In PSP and CBD, one of the most tractable treatment strategies is to block the hyperphosphorylation of tau since this is the step that blocks tau from binding to microtubules and thus prevents the resultant microtubule instability and transport impairment. Therefore, one therapeutic approach is protein kinase inhibitors that inhibit tau phosphorylation. Like other neurodegenerative conditions, strategies that promote tau clearance through proteolytic and/or autophagosomal degradation pathways are also under consideration. Anti-tau immunization has been attempted in transgenic mice with encouraging early data. Interfering with splicing machinery to decrease the 4R:3R ratio might be another approach.

Further Reading

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