What's New in Progressive Supranuclear Palsy?

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In this article we review recent developments in understanding and treating Progressive Supranuclear Palsy (PSP). Although relatively uncommon, it is an important disease both in terms of severity and progression for patients, and its characteristic tau-pathology which has much to teach us about other diseases associated with tau pathology, including Pick's disease and Alzheimer's disease.

Phenotype and prevalence

Clinically, PSP often presents with akinetic-rigidity, falls and a supranuclear vertical gaze palsy. However, cognitive impairment including apathy and executive dysfunction are common even in the early stages and were recognised in the earliest reports of PSP. Early dementia is unusual. Recognising cognitive impairment and retained cognitive abilities (despite speech and writing problems) is essential for good holistic management of patients and their carers. For example, it facilitates patients' role in decisions about their own care, and may help carers adjust to changing behaviour. Typically, PSP causes mild to moderate problems with verbal fluency, flexibility of thought and impulse control, but without marked memory impairment. Recent evidence also points to impaired recognition of emotions, an important aspect of cognition and highly relevant to dependent patients with poor communication.[1] Although the term 'subcortical dementia' has been used for PSP, it is misleading as cortical pathology and cortical atrophy contribute to cognitive deficits.

The prevalence of PSP has been estimated at 5-7 per 100,000 in epidemiological studies.[2] However, the pathology of PSP may be more common than the clinical syndrome. For example, in 277 adults with longitudinal motor and neuropsychological assessment, five cases of PSP pathology were found with no relevant symptoms or objective motor and cognitive phenotype in life.[3] Confirmation in population representative cohorts with prospective clinical data will be important to determine the true clinical and pathological prevalence of PSP. Approaching the problem from the opposite direction, by examining retrospectively records of cases with pathological proven PSP, Williams et al found approximately half of those with PSP pathology had a clinical syndrome of PSP, the other half had the syndrome of Parkinson's disease.[4] The authors distinguished PSP-Richardson's Syndrome (PSP-RS: with a classical PSP phenotype) from PSP-Parkinson (PSP-P: with a phenotype resembling Parkinson's disease). This greatly increases the likely prevalence of PSP pathology, and work is now under way to distinguish PSP-P from Parkinson's disease in lifetime.
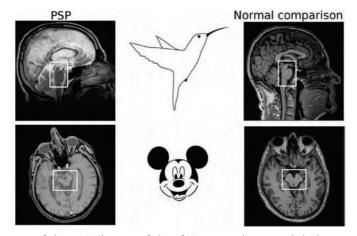
Pathology

The pathology of PSP is characterised by aggregations of the microtubule associated protein tau (MAPT or 'tau'). Typical findings on histology are tufted astrocytes, neurofibrillary tangles and argyrophilic tau-positive inclusions with a predominantly subcortical distribution and associated severe midbrain atrophy. A lifetime diagnosis of PSP is associated with its characteristic tau pathology in over 90% of cases.[5] The aetiological role for tau aggregation, rather than a bystander effect, is supported by genetics (below) and the correlation between severity of disease and density of pathological tau in the substantia nigra, caudates and dentate nucleus.[6] Interestingly, PSP is not associated with accumulation of aggregates of other key proteins linked to neurodegenerative disease, such as beta-amyloid, alpha-synuclein, ubiquitin and TDP-43. In terms of protein aggregation PSP represents a consistent and relatively pure tauopathy, in contrast with Alzheimer's disease and Pick's disease. A role for inflammation in the pathogenesis of PSP remains possible, in line with other major neurodegenerative diseases.

The nosology of PSP and related disorders is complex, reflected in an ongoing debate between 'lumpers' and 'splitters'. There is a close relationship between PSP and other syndromes associated with tau pathology, including CBD and Progressive Non-Fluent Aphasia (PNFA) within the spectrum of frontotemporal degeneration. Indeed, some patients may change clinical phenotype and diagnosis during the course of their illness. The cross-over of symptoms and similarities in pathology is sometimes reflected in a generic term 'tauopathy'. The pathology of PSP can be particularly difficult to distinguish from CBD, leading some to group these disorders within a single clinicopathological spectrum.[7] Conversely, it has been proposed PSP-PNFA represents a separate subdivision of PSP alongside Richardson's syndrome, PSP-parkinsonism, PSP-Primary Akinesia with Gait Freezing (PAGF), and a PSP-Cortcobasal Syndrome (CBS).[4] Both sides of this debate have valid points, and it is important not to let these issues stand in the way of a patient's need for a clear diagnosis and management plan.

Genetics

An association of the H1 MAPT-haplotype with PSP has been known for many years and rare families with MAPT mutations causing PSP-like syndromes have been identified. While a role for tau in the aetiology of cognitive impairment in Parkinson's disease exists,[8] a link to cognitive decline is not established for PSP. A recent major advance has been the genome-wide association study of 2065 people with PSP (and 3816 control

Imaging findings in PSP: Characteristic findings of PSP on structural imaging are the 'Mickey mouse' sign (axial slices) and the 'humming bird' sign (on sagittal slices). Imaging may also exclude hydrocephalus, extensive vascular disease, signs of normal pressure hydrocephalus and mass lesions.

subjects). In addition to two independent variants of the tau gene on chromosome 17, three new susceptibility loci were identified.[9] The new genes implicate proteins involved in vesicle-membrane fusion, the Golgi-endosomal interface and a myelin structural component. These results do not support clinical diagnostic testing for PSP, but open up the possibility of identifying critical causal pathways for PSP and novel therapeutic targets.

Treatments

The strong association of tau pathology with PSP has supported the development of novel therapies aimed at altering hyperphosphorylation and aggregation of tau. One approach is to inhibit tau phosphorylation via GSK-3b kinase. This has led to potential new uses for old drugs (e.g. lithium, valproate) as well as new compounds. A phase II trial of lithium as a GSK-3b inhibitor was stopped early due to poor tolerability (Clinical trials identifier NCT00703677). Other GSK-3 inhibitors currently in phase II trials are NP031112 (Tideglusib, Noscira, NCT01049399) and sodium valproate (Depakine, NCT00385710). Alternatively, one might stabilise microtubule function by the synthetic octapeptide intranasal NAP and a phase II trial has recently finished recruitment with ongoing follow-up (Davunetide, Allon Therapeutics, NCT01110720). Other compounds such as Paclitaxel have been found to stabilise microtubules in a cellular model of PSP, but without preventing neuronal loss.[10] It has not yet been taken forward to clinical trials.

Many other approaches to arrest neurodegeneration have been proposed. Riluzole has neuroprotective properties and prolongs disease survival in motor neurone disease. However, a phase III trial of Riluzole (NNIPPS study) showed no effect of treatment in PSP or Multiple System Atrophy (MSA).[5] Growth-colony stimulating factor has been suggested to counteract neuronal degeneration, enhance plasticity and promote migration of stem cells to damaged areas in PSP and similar diseases, although no benefit was seen in a small phase II trial of subjects with PSP, MSA and CBD.[11] Supporting mitochondrial function is thought to help slow down neurodegenerative processes; a phase II trial of coenzyme Q10 showed encouraging results[12] and a second trial is now underway (NCT00382824). A combination of creatine, pyruvate and niacinamide has also been proposed to support mitochondrial function in a forth-coming phase II trial (NCT00605930). A phase III trial examining the effect of the monoamine oxidase inhibitor Rasagaline on disease progression is recruiting participants (NCT01187888), and this might have symptomatic as well as disease-modifying effects. Finally, a small non-pharmacological study using Transcranial Magnetic Stimulation (TMS) to modulate cortical excitability is underway (NCT01174771).

The range of new disease-modifying treatments under investigation means that the next few years may see a transformation in the treatment options and prognosis of people with PSP. If these new agents are effective at slowing progression, it will place even greater emphasis on the need for better early diagnosis and symptomatic treatment.

Table 1: clinical phenotypes and extended nomenclature of syndromes related to PSP.	
Acronym	**Clinical Features**
PSP	Typical presentation with symmetrical onset of truncal rigidity, bradykinesia, early falls and supranuclear gaze palsy. Cognitive impairment (apathy, dysexecutive) common.
PSP-RS (Richardson's Syndrome)	In post mortem series, some cases had presented with the classical features of PSP as described by Steele, Richardson and Oslewski (above). This subtype was called PSP-RS.
PSP-P (Parkinsonism)	Many post mortem cases of PSP had presented with a clinical picture that resembled idiopathic Parkinson's disease. This subtype has been named PSP-P. It remains to be shown whether these cases can be prospectively identified (in life) as being distinct from Parkinson's disease.
PAGF (Pure Akinesia with Gait Freezing)	These patients present with akinesia and gait freezing in the absence of other features. Resistant to dopamine medication, and may progress with or without the emergence of other features of PD or PSP.
PIGD (Postural instability and gait disorder)	Postural instability, falling, freezing and difficulty walking may represent a prodrome of PSP or a subtype of Parkinson's disease. Often associated with cognitive impairment and resistant to dopaminergic therapy.
PSP-CBS (Corticobasal Syndrome)	Occasionally patients with PSP develop features of corticobasal degeneration (and vice versa). Clinical features may include asymmetric dystonia, alien limb, apraxia or cortical sensory loss in addition to typical features of PSP. Note that these are exclusion criteria under the NINDS-SPSP clinical diagnostic criteria for PSP (Litvan et al, 1996).
PSP-PNFA (Progressive Non-Fluent Aphasia)	Uncommon presentation with non-fluent speech, with other PSP features developing later in the disease process.
Pick's disease complex	PSP, corticobasal degeneration, non-fluent aphasia and frontotemporal lobar degeneration have many overlapping clinical features. A patient's phenotype may evolve within this group of diseases over time, leading some to propose the generic term of Pick's disease complex.

Imaging

Midbrain atrophy in PSP causes characteristic 'hummingbird' and 'Mickey mouse' signs on magnetic resonance imaging in many patients. However, clinical imaging is mainly motivated by exclusion of other pathologies (eg. vascular disease, hydrocephalus). In the research setting, imaging has confirmed patterns of cortical and subcortical atrophy.[13] MRI based functional connectivity has suggested abnormal thalamic connections within the brainstem may be responsible for the imbalance and falls in PSP.[14] In addition, positron emission tomography (using the ligand [11C] N-methylpiperidin-4-yl acetate) indicates decreased thalamic cholinergic function in PSP.[15]

Care pathway

Despite progress towards disease modification, the mainstay of PSP management remains supportive. The UK PSP Association (www.pspeur.org) is currently consulting on a model for improved standards of care, to ensure that the needs of people affected by PSP are adequately addressed. This is anticipated early in 2012. Ideally, early and correct diagnosis by a specialist would lead to comprehensive support from an integrated multidisciplinary team (including physiotherapists, speech and language therapists, occupational therapists, dieticians and specialist nurses) in liaison with social services, community based nurses and lay organisations. One feature that has often been overlooked is the need for specialist palliative care, including placing patients on palliative care registers such as the Gold Standards Framework (www.goldstandards framework.org.uk). This is likely to improve in the next few years. The PSP association is a useful resource for patients, carers and professionals alike, through online publications, specialist nurses and training, and a network of local meetings.

Summary

In summary, PSP is a fascinating and important neurodegenerative disease whose prevalence may have been underestimated. There is rapid progress in clinical, genetic and therapeutic research that will not only benefit people affected by PSP, but also the broad range of neurodegenerative diseases in which tau pathologies are implicated. ◆

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