50 Years of Progressive Supranuclear Palsy

PSP Look-alikes
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Summary
A variety of diverse disorders may cause a PSP-like phenotype, e.g. a clinical picture that resembles Richardson’s syndrome. A correct diagnosis has important clinical and research implications; some of the PSP-look alikes may be treatable, or have a different prognosis from PSP; some others may be inherited, and their identification will allow genetic counselling or offer important pathophysiological clues for sporadic PSP. The diagnosis of these PSP-look alikes is often simple, by identifying features unusual for sporadic PSP, such as earlier age of onset, unusual associated features or positive family history. Genetic conditions that may present with a PSP phenotype include MAPT, PGRN, C9ORF72 and DCTN1 mutations carriers. When the age of onset (too early), the tempo of evolution (too rapid) and the associated features (other signs such as prominent ataxia) are atypical for PSP, one should also consider disorders that may be (partially) treatable such as Whipple’s, Niemann-Pick C and paraneoplastic syndromes. However, the major diagnostic problems are caused by other sporadic neurodegenerative conditions and mainly other tauopathies, such as CBD and FTD. For the differential diagnosis of these conditions, there are still no clinical signs or biomarkers to accurately predict pathology.

Neurodegenerative disorders
The typical phenotype of patients with mutations in genes causing frontotemporal lobar degeneration (FTLD) is the behavioural variant (bvFTD), but mutations in a number of other genes have been identified to cause FTD-parkinsonism phenotypes. PSP phenotypes have been mainly associated with microtubule-associated protein tau (MAPT) and progranulin gene (PGRN) mutations [tau and TDP-43 pathology, respectively], both inherited in a dominant pattern.

The age at onset in MAPT mutation carriers is between the 3rd to 5th decade (range: 25-65 years), thus earlier than the mean age of onset in PSP (63 years). A positive family history of parkinsonism or dementia is almost always present in MAPT mutation carriers, as their penetrance is almost 100%, and they are rare in sporadic disease, although the first de novo mutation has been recently described. Early episodic memory impairment, prominent behavioural problems and semantic dementia are prevalent in patients with MAPT mutations, and may precede the onset of motor symptoms.

The mean age at onset in PGRN mutations carriers is 60 years (range: 35-83 years). PGRN mutations reach a penetrance of 90% at age 70, so a positive family history is not always present. PGRN mutations carriers usually show signs of parietal lobe involvement (e.g. dyscalculia, limb apraxia etc.) and progressive non-fluent aphasia (PNFA), which are unusual for sporadic PSP. Hallucinations may occur in up to 25% of patients with PGRN mutations and may be another helpful clue, as they rarely occur in sporadic PSP or in MAPT mutation carriers.

Hexanucleotide expansions in chromosome 9 open reading frame 72 (C9ORF72) (TDP-43 pathology) cause FTD-amyotrophic lateral sclerosis (ALS) overlap syndromes. 35% of these patients may also have atypical parkinsonism, and cases with slowness of vertical saccades, parkinsonism, frontal dementia and abnormal DaTSCANs, mimicking PSP have been reported.
Perry syndrome is a rare autosomal dominant disorder due to mutations in the dynactin (DCTN1) gene underpinned pathologically by TDP-43 inclusions. The age of onset ranges from 30-61 years. The penetrance is close to 50%. The typical phenotype includes parkinsonism with varying combinations of central hypoventilation, weight loss, and psychiatric symptoms (e.g. apathy, hallucinations). Response to levodopa varies from no response to significant improvement and development of motor fluctuations and dyskinesias. Recently, dynactin mutations have been described in families with a PSP-phenotype.  

Other disorders that may present typically with supranuclear gaze palsy comprise Kufor-Rakeb syndrome due to ATP13A2 mutations, a rare autosomal recessive disorder, characterized by juvenile-onset (12–29 years), levodopa-responsive parkinsonism (with fluctuations and dyskinesias), vertical SGP, cognitive dysfunction (dementia and visual hallucinations) and pyramidal signs. Further characteristic features include oculogyric dystonic spasms and facial-faucial-finger mini-myoclonus. T2*-weighted MRI imaging may show evidence of brain iron accumulation in some patients, which can be a helpful clue to suspect this disorder. Westphal variant Huntington’s disease may present with parkinsonism and slowness of saccades, however, the age of onset in these disorders, is too young for PSP, and do not really pose diagnostic dilemmas.

**Neuro-metabolic disorders**

Niemann-Pick C is an autosomal recessive lysosomal lipid storage disorder characterized by accumulation of unesterified cholesterol and glycolipids in the endosomal/lysosomal system. Biochemical diagnosis of Niemann-Pick C is made by filipin staining of cultured skin fibroblasts, with subsequent confirmation of the diagnosis made by mutation analysis of the NPC1 (the majority) and NPC2 genes. Miglustat is the only approved treatment for the neurologic manifestations of the disease, and patients who begin treatment early respond better, highlighting the need for early diagnosis. The adult-onset neurological form is infrequent and can present within the 2nd or 3rd decades in most patients (up to 54 years). The most common neurological features include vertical supranuclear gaze palsy, cerebellar ataxia, dysarthria, dysphagia, cognitive dysfunction and psychiatric symptoms.

Gaucher’s disease is an autosomal recessive lysosomal storage disorder caused by mutations in the glucocerebrosidase (GBA) gene, leading to deficiency of the enzyme b-glucosidase. It is more prevalent in Ashkenazi Jews. Diagnosis can be made by measuring GBA activity in leukocytes (low) and plasma chitotriosidase (high), and subsequent testing of the GBA gene. Enzymatic replacement therapy (alglycerase, imiglucerase), and substrate reduction therapy with miglustat are available treatments, without which the outcome of Gaucher’s disease is extremely unfavourable. Adult-onset parkinsonism from the 3rd to the 7th decade has been documented in Gaucher’s disease 1 and 3. Patients usually have slow horizontal saccades and increased latency launching horizontal saccades. However, some Gaucher’s disease patients with prominent slowness of vertical saccades and cognitive dysfunction, mimicking PSP, have been reported. Systemic associated features such as splenomegaly, hepatomegaly, bone crisis, bone pain, anaemia and thrombocytopenia are helpful diagnostic clues.

**Prion disorders**

Genetic Creutzfeldt–Jakob Disease (gCJD) has been linked to a variety of mutations within the prion protein gene (PRNP). Patients with disease onset between their 5th and 7th decade, vertical SGP, ‘worried facial appearance’, postural instability, axial rigidity and frontal dementia
mimicking PSP, have been described in gCJD, mostly with the E200K but rarely also with further mutations and in sporadic CJD.

References: