Available online at
ScienceDirect
www.sciencedirect.com

Elsevier Masson France
EM|consulte
www.em-consulte.com

Movement disorders

# Progressive supranuclear palsy and corticobasal degeneration: Diagnostic challenges and clinicopathological considerations

A. Eusebio [a,b,*], L. Koric [c], O. Félician [c], E. Guedj [c,d,e], M. Ceccaldi [c], J.-P. Azulay [a,b]

[a] Service de neurologie et pathologie du mouvement, CHU Timone, AP–HM, 264, rue Saint-Pierre, 13385 Marseille cedex 05, France
[b] UMR 7289, CNRS, institut de neurosciences de la Timone, Aix-Marseille université, 264, rue Saint-Pierre, 13385 Marseille cedex 05, France
[c] Service de neurologie et neuropsychologie, CHU Timone, AP–HM, 264, rue Saint-Pierre, 13385 Marseille cedex 05, France
[d] Service central de biophysique et médecine nucléaire, CHU Timone, AP–HM, 264, rue Saint-Pierre, 13385 Marseille cedex 05, France
[e] Cerimed, Aix-Marseille université, boulevard Jean-Moulin, 13005 Marseille, France

INFO ARTICLE

*Article history:*
Received 23 March 2016
Received in revised form
4 July 2016
Accepted 12 July 2016
Available online 22 August 2016

*Keywords:*
Progressive supranuclear palsy
Corticobasal degeneration
Tauopathies
Atypical parkinsonism
Clinicopathological correlations
Behavior

ABSTRACT

Progressive supranuclear palsy (PSP) and corticobasal degeneration (CBD) are two atypical parkinsonian syndromes first described half a century ago. The spectrum of these conditions as well as, more generally, the concept of tauopathy have dramatically changed over the past decade and especially in recent years. In particular, clinicopathological correlations have led to the description of several subtypes of these diseases and the features they share with other neurodegenerative diseases. The present paper is a review of how the concepts of PSP and CBD have evolved over time. In particular, it focuses on the different presentations of the disease and the overlapping syndromes that can complicate the differential diagnoses. Also discussed are some of the tools that may prove useful in making a diagnosis. Indeed, differential diagnosis issues are of particular importance in light of the likely emergence of pathology-specific disease-modifying therapies in the near future.



* *Corresponding author*. Department of neurology and movement disorders, CHU Timone, AP–HM, 264, rue Saint-Pierre, 13385, Marseille cedex 05, France.
*E-mail address:* alexandre.eusebio@ap-hm.fr (A. Eusebio).
http://dx.doi.org/10.1016/j.neurol.2016.07.009
0035-3787/

## 1. PSP and CBD of predominantly motor expression

### 1.1. *Progressive supranuclear palsy*

Progressive supranuclear palsy (PSP) was first described by Steele, Richardson and Olszewski in 1963 as a progressive neurodegenerative disorder characterized pathologically by neuronal loss, granulovacuolar degeneration, gliosis and neurofibrillary tangles in the basal ganglia, brainstem and cerebellar nuclei [1–3]. The classic presentation of PSP associates a predominantly axial parkinsonism, supranuclear gaze palsy and postural instability with early falls [4]. Rigidity and bradykinesia tend to respond minimally and transiently to dopamine replacement therapy. Swallowing and chewing difficulties causing aspiration and/or weight loss also frequently appear over time. However, of all features of the disease, falls are the most dramatic expression because of their precocity in the course of the disease and the frequent inability of the patient to take any effective protective action when they happen. Thus, falls often have severe traumatic consequences and are one of the main causes of death, along with aspiration, and the early appearance of falls has been associated with a poorer prognosis [2,4,5].

Two sets of validated diagnostic criteria are available: the National Institute of Neurological Disorders and Stroke (NINDS) and the Society for PSP (SPSP). Both criteria separate patients into two diagnostic categories: possible PSP, which has high sensitivity and average specificity; and probable PSP, which has high specificity and average sensitivity for PSP pathology [2]. The more recently published Neuroprotection and natural history in Parkinson's plus syndromes (NNIPPS) criteria [6] have a similar profile to the NINDS–SPSP criteria for probable PSP [7]. The age-adjusted prevalence of PSP is five cases per every 100,000 [8,9]. The mean age at onset is 63 years, and the mean survival varies between 6 and 9 years from disease onset, with patients going undiagnosed for up to half that duration of time [2,10–12].

In addition to the motor features described above, patients with PSP also develop cognitive and behavioral impairments, which may sometimes predominate at onset or over the course of the disease (see the next main section below).

Apart from levodopa, which may transiently and inconsistently improve motor symptoms, other treatment options can help to reduce some of the symptoms, such as botulinum toxin particularly for blepharospasm and eyelid apraxia. However, none of these therapeutic approaches leads to dramatic symptom improvement. In addition, as no disease-modifying or neuroprotective therapy is currently available, patients therefore often receive mostly non-medical care, such as physio- and speech therapy.

Over the past decade, accumulating clinicopathological evidence has led to the description of several additional clinical syndromes associated with PSP pathology (Fig. 1) [13–15]. The classic phenotype described above has been termed ''Richardson's syndrome'' (PSP-RS). PSP parkinsonism (PSP-P) is characterized by bradykinesia, rigidity, and a postural and sometimes rest tremor that tends to be asymmetrical and at least modestly responsive to levodopa therapy, which can lead to misdiagnoses of the condition as Parkinson's disease. This presentation, which affects up to 30% of patients with PSP pathology, later progresses to the postural/gait, cognitive and oculomotor impairments described in PSP-RS. Due to the later development of postural instability, however, this form progresses more slowly than PSP-RS, with death occurring, on average, 8–11 years after disease onset [15].

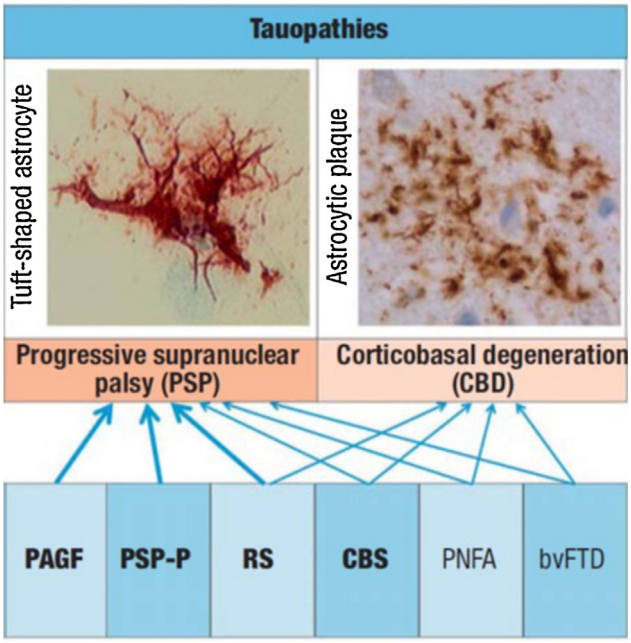


**Fig. 1 – Clinical syndromes associated with progressive supranuclear palsy (PSP) and corticobasal degeneration (CBD) pathology. PAGF: pure akinesia with gait freezing; PSP-P: PSP and parkinsonism; RS: Richardson's syndrome; CBS: corticobasal syndrome; PNFA: progressive non-fluent aphasia; bvFTD: behavioral variant of frontotemporal degeneration.**
**Modified from Levin et al. [163].**

Another PSP variant, known as ''pure akinesia with gait freezing'' (PSP-PAGF), is characterized by the progressive onset of difficulty in gait initiation and later freezing of gait, and speech and writing difficulties. There is no appendicular rigidity (although axial rigidity may be seen) and no tremor, oculomotor or cognitive impairment during the first 5 years of the condition. Dopamine replacement therapy is ineffective. Progression of the disease sees a gradual worsening of postural and gait disorders, causing the patient to eventually become wheelchair-bound. Oculomotor and swallowing impairment may also arise late in the course of disease, whereas cognitive function is rarely affected. Death occurs, on average, 11 years after disease onset [15].

Progressive speech apraxia evolving into progressive non-fluent aphasia (PNFA) may be the presenting sign of the PSP-PNFA variant. This subtype, described in detail in a next main section, may have no aspects of classic PSP associated with the speech/language impairment, at least not early in the disease course [15].