

## Mini Review

# Progressive Supranuclear Palsy Cerebellar Variant

Harini Sarva\*

Department of Neurology, Maimonides Medical Center, USA

## Corresponding author

Harini Sarva, Department of Neurology, Maimonides Medical Center, 883 65th Street, Brooklyn, NY 11220, USA, Tel: 7182837470; Fax: 7186356082; Email: sarvaharini@gmail.com

Submitted: 26 May 2016

Accepted: 07 June 2016

Published: 10 June 2016

ISSN: 2333-7087

## Copyright

© 2016 Sarva

## OPEN ACCESS

## Keywords

- Progressive supranuclear palsy
- Cerebellar variant
- Dentate nucleus
- Superior cerebellar peduncle

## Abstract

Progressive Supranuclear Palsy (PSP) is an atypical Parkinsonism noted for postural instability, early falls, and a supranuclear vertical gaze palsy. However, since its original description, several variants were described. One of the rarer variants is PSP-C, further adding to the diverse clinical. As a result, misdiagnosis of PSP-C as multiple system atrophy, or a spinocerebellar degeneration is not uncommon. Accurate antemortem diagnosis would prove invaluable not only for prognostic implications but also for development of potential treatments.

## ABBREVIATIONS

PSP: Progressive Supranuclear Palsy; PSP-C: Progressive Supranuclear Palsy-Cerebellar Variant; MSA: Multiple System Atrophy; RS: Richardson's Syndrome; PSP-P: Progressive Supranuclear Palsy-Parkinsonism

## INTRODUCTION

Progressive supranuclear palsy, first described by Steele et al, [1] is an atypical parkinsonism characterized by supranuclear vertical gaze palsy, dysphagia, dysarthria, balance problems, falls, and cognitive impairment [1,2]. Prevalence is estimated at 6-7 cases per 100000 [3]. Pathologically, PSP is defined by accumulation of tau protein and neuropil threads in the subthalamic nucleus, red nucleus, pallidum, striatum, substantia nigra, pontine tegmentum, medulla, oculomotor nucleus, and dentate nucleus [3]. The National Institute of Neurological Disorders and Stroke and the Society for Progressive Supranuclear Palsy (NINDS-SPSP) [4] workshop proposed the following diagnostic categories: possible, probable, and definite PSP. Age of onset over the age of 40, gradual progression, and lack of other neurological disorders are required for all categories. Possible PSP requires downward or upward vertical gaze palsy or both slow vertical saccades and prominent postural instability with falls in the first year of onset. Probable PSP requires vertical gaze palsy and postural instability with falls within the first year. Definite PSP requires histopathological confirmation. Exclusion criteria included recent encephalitis, cortical phenomena (alien hand syndrome), hallucinations or delusions unrelated to dopaminergic therapy, Alzheimer's dementia, prominent and early cerebellar features, severe asymmetric parkinsonism, prominent autonomic dysfunction, neuroradiologic evidence of basal ganglia or brainstem infarctions, and evidence of Whipple's disease confirmed by polymerase chain reaction. Supportive criteria included symmetric akinesia and rigidity affecting proximal more than distal musculature, retrocollis,

early dysphagia and dysarthria, and early onset of cognitive impairment [4]. Since these criteria were developed, several different variants were described: Richardson's Syndrome (symmetric axial rigidity, supranuclear gaze palsy, retrocollis, apathy, intellectual slowing); PSP-parkinsonism (asymmetric, indolent Parkinson's disease features with a transient response to levodopa); PSP-pure akinesia with gait freezing (pronounced gait freezing but without tremor, rigidity, dementia, or eye movement abnormalities within the first five years); PSP-progressive non-fluent aphasia (non-fluent speech, phonemic errors, hesitancy, and agrammatism); PSP-C (prominent, early cerebellar signs); and PSP-corticobasal syndrome (progressive, asymmetric dyspraxia, alien limb phenomena, jerky dystonia, cortical sensory loss, or severe bradykinesia unresponsive to levodopa) [3]. However, these distinctions are not well established; thus, prevalence of these subtypes may vary considerably. A multicenter autopsy study of 100 pathologically confirmed PSP cases demonstrated that 24% were classic RS and 76% were atypical cases, suggesting that the NINDS-SPSP criteria has low sensitivity but high specificity for diagnosis [5]. PSP-C specifically is quite rare and its frequency among several studies varies considerably [2]. In this mini review, the epidemiology, clinical features, and pathology of PSP-C are discussed.

## Clinical variability of PSP

Since its first description, in which four of nine cases had cerebellar features [1], several pathologically proven studies of PSP assessed its clinical variability [6-10]. A study of 12 cases [6] demonstrated that postural instability and falls were present in all patients and were an early feature. Downgaze paresis was not present in half during the early phase and at last neuro-ophthalmological examination, two patients never developed vertical gaze palsy. Cerebellar type limb ataxia was found in only one. Symmetric features of RS were not found in all and half had asymmetric signs. Of note 8/12 were correctly diagnosed as PSP antemortem [6]. In another series of 16 cases, balance or gait

difficulty was the initial presentation in nine [7]. Only four were correctly identified as PSP within three years of onset. One case was initially diagnosed with a spinocerebellar ataxia prior to death [7]. Other eye movements apart from supranuclear vertical gaze palsy should alert physicians to PSP: slowed downward command saccades, failure to suppress the vestibular reflex, absent Bell's phenomena, apraxia of eyelid opening, and square-wave jerks [7]. In a study of 103 cases, two major phenotypes were demonstrated: 54% with RS and 32% with PSP-P [8], one percent had cerebellar features [8].

Kanazawa et al., [9] proposed the classification of a PSP cerebellar variant after their study of 22 cases demonstrated three with cerebellar ataxia and pathologically pronounced cerebellar degeneration [10]. A subsequent Austrian study of 30 cases (18 with RS and 12 with PSP-P) did not reveal early predominant cerebellar signs [11]. Two in the RS group (6.7%) developed cerebellar signs late in their course, however [10]. An American study [2] of 1085 cases identified five patients as having PSP-C. Thus, PSP-C is a rare clinical variant in the United States with a frequency of about 1%, similar to other Western countries and less compared with Japan [2,12]. It is possible that the underreporting of PSP-C may be due to the masking of cerebellar features by the severe akinesia and rigidity that eventually develop [13]. It is also possible that other features may be mistaken for ataxia such as apraxia, dystonia, or instability due to a sensory neuropathy. It is not uncommon in patients with neurodegenerative disease to have other comorbidities such as cerebrovascular disease or peripheral neuropathy which may lead to ataxic symptoms and possible over-reporting of ataxia [2]. Although these pathological studies provide us with an opportunity to study confirmed cases of PSP, they are quite limited. They rely on retrospective descriptions of clinical findings and many did not have video confirmation of the examinations, relying heavily on the examiner's written descriptions. Also, they rely on brain banks from major academic centers which lend themselves to selection bias, as the most atypical cases are often included [2,5]. Though adding to our understanding of PSP, they describe various subtypes without consensus definitions.

### Diagnosis of PSP-C

PSP-C commonly occurs in older men with an average duration of six years. Initially gait impairment and truncal ataxia occur. Falls and supranuclear gaze palsy appear within two years of onset and there is no significant dysautonomia [12].

Formal diagnostic criteria of PSP-C based on clinical features which developed in the first two years of disease and MRI findings in four pathologically proven cases [14] include the following: A) slowly progressive course; B) age greater than 40 years; C) supranuclear gaze palsy; D) truncal and limb ataxia developing within two years of symptom onset; and E) postural instability with falls within two years of symptom onset. Exclusion criteria include profound dysautonomia and hot cross bun sign on MRI. Probable PSP-C requires all of the above inclusion criteria. Possible PSP-C requires A+B+D+E [14]. Thus, adequately diagnosing antemortem PSP-C requires cerebellar features to be predominant within the first two years of onset. However, not all of the PSP-C cases in the American series met all the required diagnostic criteria [2]. Early falls and vertical gaze palsy were

less frequent in PSP-C. Three had mild autonomic symptoms, two with urinary incontinence and another with intermittent syncope. Eye movement abnormalities were also varied, with one having frank supranuclear vertical gaze palsy and two with slow saccades. Two had normal eye movements of the five cases, one had probable and three had possible PSP-C [2]. These inconsistent results further support the need for consensus definitions and their validation as it is possible these patients did not have PSP-C. They may have been misclassified as PSP-C due to the presence of cerebellar features noted at other stages of disease. This is suggested by the development of some degree of cerebellar ataxia in 39% of PSP patients in one study [2]. In another study of 134 patients [9], three of 15 PSP cases developed cerebellar ataxia at the onset while four others developed ataxia of gait, limbs, or speech later in the disease course of disease [9]. Another study also had cases with early development of cerebellar features characteristic of PSP-C with others developing ataxia later in the course (inconsistent with PSP-C criteria) [15].

In an effort to better classify PSP, The Natural History and Neuro protection in Parkinson Plus Syndromes (NNIPPS) study developed antemortem diagnostic criteria, which had a very high sensitivity and specificity when compared with their pathological diagnoses [16,17]. These criteria define PSP as having supranuclear ophthalmoplegia and postural instability or falls developing within the first three years of disease. Although they improved antemortem diagnosis in their study of over 600 patients, cerebellar features could not be reliably assessed. These criteria are however still not commonly used in clinical or research practice but are under further review [16,17].

### Pathological and imaging evidence of cerebellar pathology

Kanazawa et al., noted a high number of tau-positive inclusion bodies in Purkinje cells in those with cerebellar involvement compared with those without cerebellar ataxia, [11]. A subsequent pathological report of a 69 year-old man with ataxic gait demonstrated atrophy of the frontotemporal lobe, brainstem, and cerebellum [18]. Cerebellar atrophy was most noted in the white matter and dentate nucleus. Microscopically, neurofibrillary tangles were prominent in the cerebral cortex, basal ganglia, brainstem, and inferior olivary nucleus, and cerebellar dentate nucleus. The dentate nucleus also had severe gliosis. Superior cerebellar peduncles were atrophic, particularly on the right side. Purkinje cells contained tau-positive inclusions. Olivopontocerebellar degeneration (OPCA) was greater than other known, typical PSP cases but less than in other causes of OPCA [18]. Diffuse cytoplasmic, phospho-tau immunoreactivity, tau-positive thread-like processes, and coiled bodies or oligodendroglial tau-positive inclusions were present in the cerebellar dentate nucleus or cerebellar white matter in the PSP-C cases from the Mayo Clinic patient series [2]. Despite the presence of cerebellar pathology in these cases, a direct relationship between cerebellar degeneration and clinical signs could not be established [2,11]. In one series, 99 cases of PSP had similar tau-positive inclusions in the dentate nucleus as those found in the PSP-C cases. Three of five with PSP-C and 61 of 97 PSP patients had cytoplasmic phospho-tau immunoreactivity but without obvious NFT formation. Linear density of Purkinje cells was not different between the two groups. There were

no significant differences in the burden of tau pathology in the cerebellar afferent system, cerebellum, and basal ganglia. Thus, no correlation between the frequency of cerebellar ataxia and the severity of cerebellar pathology was found [2], particularly when the definition of PSP-C is so variable. Thus, further study into the exact pathological changes which specifically contribute to the development of PSP-C as opposed to the pathological changes seen in PSP in general such as involvement of cerebellar dentate nucleus, is required. Its involvement across all subtypes suggests that it is not a reliable causative marker for PSP-C and is likely a result of PSP being a multi-network disease.

Radiologic characteristics were studied in a single case of a 72 year-old Japanese man with PSP-C who had serial MRI's [19]. Initial MRI was unremarkable but a MRI performed two years later showed dilatation of the pontocerebellar cistern and atrophy of the superior cerebellar peduncles. A third MRI performed four years after symptom onset showed increased dilatation of the pontocerebellar cistern, proportional but small pons and cerebellum with fourth ventricular dilatation, and rostral midbrain atrophy. Quantitative analysis demonstrated that the dilated pontocerebellar cistern occupied more of the posterior fossa space with each MRI: first (12.6% of posterior fossa); second (20% of posterior fossa); and third (29.9% of posterior fossa). Although the cistern was enlarged the cerebellar hemispheric fissures were not progressively enlarged. The authors postulated the enlarged pontocerebellar cistern along with the relatively small pons and cerebellum to be a characteristic MRI feature [19]. Thus, this may be helpful as changes were noted in the first two years of disease, when the proposed diagnostic criteria require cerebellar features to be present. However, this radiographic finding does not directly explain the cerebellar signs as patients with minimal or no cerebellar features also have alterations of the superior cerebellar peduncle, the primary cerebellar outflow tracts, and the cerebellar dentate nucleus as shown in radiological studies using standard FLAIR MRI sequences [20], diffusion tensor imaging studies [21], and RESOLVE (Readout Segmentation of Long Variable Echo-Trains which provides higher spatial resolution) [22] as well as transcranial magnetic stimulation [23] suggesting impaired cerebellar inhibition in PSP. Thus, while radiographically cerebellar nuclei and outflow tracts may be involved, they are not specific for PSP-C and further study is needed to accurately diagnose it antemortem.

### Treatment and prognosis

There is no neurorestorative therapy for any form of PSP and treatment is symptomatic. Levodopa, cholinesterase inhibitors, and serotonin reuptake inhibitors provide modest yet inconsistent benefit [3]. Interestingly, 32% of 97 cases from a large series noted a greater than 30% improvement in symptoms from dopaminergic treatment (levodopa or dopamine agonists). However, the duration of therapy was not recorded [8]. Botulinum toxin may be used for focal dystonias [3].

PSP in general has a graver prognosis when compared with Parkinson's disease [3] but even among the variants there may be differences. Studies suggest that those with an asymmetric PD-like presentation respond more to levodopa and may actually live longer than those with classic RS [5,7,8]. Prognostic considerations in PSP-C are more limited. However, Kanazawa

et al., noted that those with the unclassified PSP (cerebellar and cortical predominance) had shorter disease duration than RS and PSP-P [11]. Interestingly, cerebellar ataxia may be self-limited as four of 28 probable PSP patients had ataxia which lasted from 13-24 months, after which typical PSP features developed [13].

## DISCUSSION & CONCLUSION

PSP-C is a rare variant of PSP, which may be more prominent in Japan. It further adds to the phenotypic variability of PSP and misdiagnosis can occur. Older age of onset, shorter disease duration and prominent early cerebellar findings within the first two years are hallmarks. Pathological and radiographic findings, though demonstrating cerebellar pathology, do not fully explain the development of the disease. Treatment remains similar to other forms and is limited. Larger studies are required to assess the true prevalence of this condition as well as appropriate treatment options.

## REFERENCES

1. Steele JC, Richardson JC, Olszewski J. Progressive Supranuclear Palsy. A Heterogeneous Degeneration Involving the Brain Stem, Basal Ganglia and Cerebellum with Vertical Gaze and Pseudobulbar Palsy, Nuchal Dystonia and Dementia. *Arch Neurol*. 1964; 10: 333-359.
2. Koga S, Josephs KA, Ogaki K, Labbé C, Uitti RJ, Graff-Radford N, et al. Cerebellar ataxia in progressive supranuclear palsy: An autopsy study of PSP-C. *Mov Disord*. 2016; 31: 653-662.
3. Barsottini OG, Felício AC, Aquino CC, Pedroso JL. Progressive supranuclear palsy: new concepts. *Arq Neuropsiquiatr*. 2010; 68: 938-946.
4. Litvan I, Agid Y, Calne D, Campbell G, Dubois B, Duvoisin RC, et al. Clinical research criteria for the diagnosis of progressive supranuclear palsy (Steel-Richardson-Olszewski syndrome): Report of the NINDS-SPSP International Workshop. *Neurology*. 1996; 47: 1-9.
5. Respondek G, Stamelou M, Kurz C, Ferguson LW, Rajput A, Chiu WZ, et al. The phenotypic spectrum of progressive supranuclear palsy: a retrospective multicenter study of 100 definite cases. *Mov Disord*. 2014; 29: 1758-1766.
6. Collins SJ, Ahlskog JE, Parisi JE, Maraganore DM. Progressive Supranuclear Palsy: neuropathologically based diagnostic clinical criteria. *J Neurol Neurosurg Psychiatry*. 1995; 58: 167-173.
7. Birdi S, Rajput AH, Fenton M, Donat JR, Rozdilsky B, Robinson C, et al. Progressive supranuclear palsy diagnosis and confounding features: Report on 16 autopsied cases. *Mov Disord*. 2002; 17: 1255-1264.
8. Williams DR, de Silva R, Paviour DC, Pittman A, Watt HC, Kilford L, et al. Characteristics of two distinct clinical phenotypes in pathologically proven progressive supranuclear palsy: Richardson's syndrome and PSP-parkinsonism. *Brain*; 2005. 128: 1247-1258.
9. Koga S, Aoki N, Uitti RJ, van Gerpen JA, Cheshire WP, Josephs KA, et al. When DLB, PD, and PSP masquerade as MSA: an autopsy study of 134 patients. *Neurology*. 2015; 85: 404-412.
10. Jellinger K. Cerebellar involvement in progressive supranuclear palsy. *Mov Disord*. 2010; 25: 1104-1105.
11. Kanazawa M, Shimohata T, Toyoshima Y, Tada M, Kakita A, Morita T, et al. Cerebellar involvement in progressive supranuclear palsy: A clinicopathological study. *Mov Disord*. 2009; 24: 1312-1318.
12. Shimohata T, Kanazawa M, Yoshida M, Saito Y, Iwai K, Yasuda T. Clinical and imaging findings of progressive supranuclear palsy with predominant cerebellar ataxia. *Mov Disord*. 2016; 31: 760-762.

13. Sawa N, Kataoka H, Kiriyama T, Izumi T, Taoka T, Kichikawa K, et al. Cerebellar dentate nucleus in progressive supranuclear palsy. *Clin Neurol Neurosurg*. 2014; 118: 32-36.
14. Shimohata T, Kanazawa M, Takahashi H, Nishizawa M. Clinicopathological features and diagnostic criteria for progressive supranuclear palsy with predominant cerebellar ataxia. *Mov Disord*. 2015; 30: 329.
15. Kanazawa M, Tada M, Onodera O, Takahashi H, Nishizawa M, Shimohata T. Early clinical features of patients with progressive supranuclear palsy with predominant cerebellar ataxia. *Parkinsonism Relat Disord*. 2013; 19: 1149-1151.
16. Bensimon G, Ludolph A, Agid Y, Vidailhet M, Payan C, Leigh PN, et al. Riluzole treatment, survival and diagnostic criteria in Parkinson plus disorders: the NNIPPS study. *Brain*. 2009; 132: 156-171.
17. Payan CA, Viallet F, Landwehrmeyer BG, Bonnet AM, Borg M, Durif F, et al. Disease severity and progression in progressive supranuclear palsy and multiple system atrophy: Validation of the NNIPPS--Parkinson plus scale. *PLoS One*. 2011; 6: 22293.
18. Iwasaki Y, Mori K, Ito M, Tatsumi S, Mimuro M, Yoshida M. An autopsied case of progressive supranuclear palsy presenting with cerebellar ataxia and severe cerebellar involvement. *Neuropathology*. 2013; 33: 561-567.
19. Kanazawa M, Shimohata T, Endo K, Koike R, Takahashi H, Nishizawa M. A serial MRI study in a patient with progressive supranuclear palsy with cerebellar ataxia. *Parkinsonism Relat Disord*. 2012; 18: 677-679.
20. Kataoka H, Tonomura Y, Taoka T, Ueno S. Signal changes of superior cerebellar peduncle on fluid-attenuated inversion recovery in progressive supranuclear palsy. *Parkinsonism Relat Disord*. 2008; 14: 63-65.
21. Blain CR, Barker GJ, Jarosz JM, Coyle NA, Landau S, Brown RG, et al. Measuring brain stem and cerebellar damage in parkinsonian syndromes using diffusion tensor MRI. *Neurology*. 2006; 67: 2199-2205.
22. Hara K, Watanabe H, Ito M, Tsuboi T, Watanabe H, Nakamura R, et al. Potential of a new MRI for visualizing cerebellar involvement in progressive supranuclear palsy. *Parkinsonism Relat Disord*. 2014; 20: 157-161.
23. Shirota Y, Hamada M, Hanajima R, Terao Y, Matsumoto H, Ohminami S, et al. Cerebellar dysfunction in progressive supranuclear palsy: A transcranial magnetic stimulation study. *Mov Disord*. 2010; 25: 2413-2419.

**Cite this article**

Sarva H (2016) *Progressive Supranuclear Palsy Cerebellar Variant*. *J Neurol Transl Neurosci* 4(1): 1062.