HHS Public Access

Author manuscript

Acta Neurol Scand. Author manuscript; available in PMC 2020 June 12.

Published in final edited form as:

Acta Neurol Scand. 2016 October ; 134(4): 242–249. doi:10.1111/ane.12546.

Progressive supranuclear palsy (PSP): Richardson syndrome and other PSP variants

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Abstract

Phenotypic heterogeneity of progressive supranuclear palsy (PSP) has been increasingly reported in the literature and can be the source of incorrect clinical diagnosis particularly in the early stages of the disease when the classically associated symptoms of early falls and supranuclear gaze palsy may not be apparent. In addition to Richardson syndrome (RS), several atypical clinical phenotypes have been described. Advances in genetic, neuroimaging, and biochemical/molecular technologies contribute to the identification of these clinical subtypes in the context of typical PSP pathological findings. Our goal is to review the phenomenology reported in the literature that is associated with confirmed histopathological changes consistent with a PSP diagnosis and to highlight the clinical spectrum of PSP. A systematic review of the literature in PubMed through July 2015 using MeSH terms and key words related to PSP was conducted. Articles describing PSP classifications, diagnostic criteria, and case reports were reviewed and summarized. Additional PSP phenotypes not seen in recent clinicopathological studies are included. These include primary lateral sclerosis, pallido-nigro-luysian degeneration, axonal dystrophy, and multiple system atrophy in the spectrum of atypical PSP variants beyond the traditionally classified PSP subtypes. This review is intended to help with the diagnostic challenges of atypical PSP variants. We believe that large multicenter clinicopathological studies will help expand our understanding of etiology and specific mechanisms of neurodegeneration and will aid in the appropriate interpretation of outcomes when conducting clinical and basic science research.

Keywords

atypical parkinsonism; phenomenology; progressive supranuclear palsy; Richardson syndrome; tauopathy

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Conflict of interest

The authors have no conflict of interest to report.

Introduction

Richardson, Steele, and Olszewski, in 1963, defined a syndrome characterized by progressive parkinsonism with early falls due to postural instability, supranuclear ophthalmoplegia primarily of vertical gaze, pseudobulbar dysfunction, dystonic rigidity of the neck and upper trunk, and mild cognitive dysfunction in a cohort of nine patients. Neuropathological findings affecting the basal ganglia, brain stem, and cerebellum were described as neurofibrillary tangles (NFTs), granulovacuolar degeneration, neuronal cell loss, and gliosis. They called this disorder progressive supranuclear palsy (PSP) (1).

Since its initial description, the clinical diagnosis of PSP and its association to specific pathological findings has become increasingly complex. Lantos first drew attention to the pathological heterogeneity of PSP when he described distinct patterns of histopathological findings and proposed dividing PSP pathological classification into PSP type 1 (typical PSP), PSP type 2 (atypical PSP), and PSP type 3 (combined pathology with other neurodegenerative disorders) (2). Since then, the pathological findings associated with a diagnosis of PSP have been identified in subjects with clinical phenotypes that vary in severity and distribution as well as in sequential appearance of specific symptomatology (3). In addition, the term ‘atypical PSP’ has also been used to describe patients who present with specific symptoms not originally described or those who do not have the complete constellation of symptoms associated with the classical diagnosis of PSP. Challenges in the clinical diagnosis of PSP are illustrated in the continuous efforts to find specific features that would distinguish Steele–Richardson–Olszewski syndrome from other parkinsonian syndromes (4).

As more phenotypic presentations associated with PSP pathology are identified, other more inclusive terminology has begun to appear in the literature. Dickson et al. (3) described different clinical and pathological features of PSP that he called major variants of PSP. The authors classified the clinical features into three distinct categories which they named ‘typical PSP’, ‘brainstem predominant’, and ‘cortical predominant’ to encompass the various phenotypic presentations. However, the use of descriptive terms to convey a pathological process (i.e., ‘brainstem predominant atypical PSP’) assists in correlating these findings to a specific clinical presentation, it does not take into account the fact that some of these clinical presentations may not have pathological findings consistent with PSP. Another descriptive term, progressive supranuclear palsy syndrome (PSPS), was introduced in the literature as a synonym for Richardson’s syndrome (5–7). Josephs et al. (5) first used the term indicating a clinical phenotype but assumed a tauopathy would be the pathological finding. In addition, Armstrong et al. (6) also proposed the use of PSPS to refer to patients with three of five symptoms/signs that did not include speech disturbances or freezing of gait, both presentations described by Dickson et al. (3) as ‘variants of PSP’. Botha et al. (7) broadened the term PSPS to be used as a clinical description, acknowledging additional phenotypes other than Richardson syndrome but also made the assumption that PSPS anticipates a pathological diagnosis consistent with PSP.

Recently, Respondek et al. (8) published a retrospective chart review of 100 cases with pathologically proven PSP, further confirming the loose association between clinical

presentation and pathological findings. They classified patients according to the predominant clinical features in the first 2 years after onset of disease manifestations and called these groups ‘PSP-predominance type’. In their study, only 24% of the pathologically proven cases had a clinical history consistent with Richardson syndrome (RS), while the remaining 76% of patients were referred to as non-RS. After a principal component analysis of symptoms reported in the first 2 years of disease, the authors described three clinical groups including patients with oculomotor dysfunction and falls, patients with parkinsonism, and patients with frontal and cognitive dysfunction. However, these clinical constellations only accounted for 37% of the pathologically proven cases.

Our aim is to describe the phenomenology of PSP reported in the literature including clinical presentations not found in recent clinicopathological reports (5, 8). All clinical presentations found in this literature review report pathological findings consistent with a diagnosis of PSP. A brief discussion of some treatment strategies has been included but an exhaustive review of all treatment modalities, neuroimaging findings, genetics, and neuropathological mechanisms is beyond the scope of this article.

PSP–Richardson syndrome (RS)

In 2005, Williams et al. identified two distinct clinical phenotypes in 103 consecutive cases of pathologically confirmed PSP. In their paper, the authors proposed the clinical classification of PSP-RS (RS) for the group of patients presenting with the characteristics originally described by Steele et al. (9). RS typically presents with early falls, early cognitive dysfunction, abnormalities of gaze, and postural instability. The authors further elaborated on these patients’ clinical characteristics to include abnormal gait described as lurching and unexplained falls backwards without loss of consciousness as a common initial presentation. Supranuclear gaze palsy is a diagnostic feature but may not occur until later in the disease course. RS is male predominant with a male to female ratio of 1.8:1. Prognosis was found to be worse in this group with a reported disease duration averaging 5.9 years (range of 5–8 years) and earlier age at death (average 72.1 years) when compared to those with PSP-parkinsonism (PSP-P) phenomenology.

PSP–parkinsonism (PSP-P)

Williams et al. introduced the term PSP-P for the group of pathologically confirmed PSP cases who had a clinical presentation of asymmetrical onset, tremor, early bradykinesia, non-axial dystonia, and who also had response to levodopa therapy. Patients with PSP-P differed clinically from those with RS mainly in initial asymmetrical onset, more frequent presence of tremor, early bradykinesia, non-axial dystonia and moderate-to-good initial response to levodopa, features that closely resemble idiopathic Parkinson disease (PD). Early bradykinesia was described to be essential for the diagnosis. Sex distribution in this group was found to be even, and disease duration was longer (9.1 years) than that seen in those with the RS phenotype (9). The authors cautioned that clinical differences between RS and PSP-P are more evident in the initial 2 years, although there is clinical overlap and after 6 years of follow–up, the clinical phenomenology might become very similar.

PSP–pure akinesia with gait freezing (PSP-PAGF)

Patients with pure akinesia and poor levodopa response have been described in the literature (10). Williams et al. (11) proposed diagnostic criteria for a third clinical phenotype that includes progressive onset of gait disturbance with start hesitation and subsequent freezing of gait, speech, or writing but without rigidity, tremor, dementia, or eye movement abnormality during the first 5 years of the disease. These patients' clinical presentation includes features of micrographia, hypophonia, and slowness of gait. Gradual onset of gait freezing associated with early back pain and nuchal rigidity was also reported. Eye movement abnormalities occurred a mean of 9 years after disease onset. Striking and consistent clinical features in patients with PSP-PAGF are gait unsteadiness and slowness that gradually evolves into difficulties with the initiation of walking and freezing of gait that are also associated with handwriting and speech difficulties. These patients do not benefit from levodopa therapy, and no clinical or radiological evidence of lacunar infarcts or diffuse deep matter ischemia was described in this cohort. This PSP phenotype was clinically differentiated from RS by the absence of cognitive dysfunction, eye movement abnormalities, and falls within the first 2 years of disease.

PSP–progressive nonfluent aphasia/apraxia of speech (PSP-PNFA/AOS)

Progressive nonfluent aphasia is a degenerative language disorder characterized by effortful speech production, phonological and grammatical errors as well as word retrieval difficulties (12). Josephs et al. (13) reported four cases with atypical PSP pathological findings that had an initial presentation of a progressive motor speech disorder that was predominantly apraxia of speech (AOS). All four patients showed a language disorder characterized by nonfluency, anomia and early preservation of episodic memory, semantic knowledge, and comprehension of language correlating to shifts in tau pathology from subcortical and brainstem structures, seen in 'typical PSP', to the neocortex.

The term PSP-AOS has been proposed due to the association of specific motor speech disorder without aphasia associated with PSP (14) and studies suggesting that the presence of PNFA may be suggestive of other pathological findings (15). However, in most of the literature reviewed, this syndrome is referred to as PSP-PNFA.

PSP–cerebellar ataxia (PSP-C)

Although cerebellar ataxia has been one of the diagnostic exclusion criteria for a diagnosis of probable or possible PSP, according to the NINDS-SPSP criteria (16), certain patients with a pathological diagnosis of PSP have predominant cerebellar features described in the literature as 'PSP with cerebellar ataxia' and PSP-C (17). After retrospective analysis of 22 pathologically confirmed Japanese patients with PSP, Kanazawa et al. described cerebellar involvement in three patients with initial onset of cerebellar ataxia clinically diagnosed as having spinocerebellar degeneration. All three patients had gait and limb ataxia early in the disease course, and one had these symptoms prior to supranuclear gaze palsy and cognitive decline. Tau-positive inclusion bodies in Purkinje cells were more frequently observed in patients with cerebellar ataxia than in those without. Iwasaki et al. recently described a

subject with initial presentation of ataxic gait and diagnosis of olivopontocerebellar atrophy. Parkinsonian features did not develop until 7 years of disease after onset, and the pathological diagnosis was consistent with PSP (18). Koga et al.'s recent report on the clinicopathological correlation of 134 cases with a clinical diagnosis of multiple system atrophy (MSA) revealed that the common reason for a misdiagnosis of MSA in patients with pathological confirmation of PSP is the presence of cerebellar ataxia (19). In their study, three patients with pathologically confirmed PSP had cerebellar ataxia as their initial clinical presentation.

PSP–corticobasal syndrome (PSP-CBS)

Recently, the term corticobasal syndrome (CBS) was introduced due to clinical presentations suggestive of CBD in patients with pathological findings not consistent with this diagnosis (20). Tsuboi et al. described the clinicopathological characteristics of five cases of pathologically proven PSP that presented with CBS, although three of the cases had additional pathological findings. The clinical observations included characteristics not typically associated with RS such as asymmetrical features, apraxia, alien limb phenomenon, and progressive aphasia. They concluded that when PSP presents as CBS, it is likely due to concurrent cortical pathology from a secondary process such as AD or from PSP pathology extending into cortical areas that are primarily affected in CBD (21).

Ling et al. (22) recently reported 10 patients with a final clinical diagnosis of CBS but pathological diagnosis of PSP. These patients exhibited strikingly asymmetrical features throughout the entire disease course including some patients with ideomotor limb apraxia, hand dystonia, alien limb phenomenon, nonfluent aphasia, cortical sensory loss, and hemisensory neglect. Many of these patients developed ocular features suggestive of RS as well as postural instability or falls within the first year of symptom onset.

PSP–behavioral variant frontotemporal dementia (PSP-bvFTD)

In recent years, PSP, CBD, and tau-positive FTD were included in FTLD-tau neuropathological subtypes of frontotemporal lobar degeneration (FTLD) (23). Frontotemporal dementia (FTD) is a clinical syndrome with three classical presentations: behavioral variant (bvFTD), nonfluent progressive aphasia (NFPA), and semantic dementia (24). The clinical characteristics of bvFTD include early symptoms of social disinhibition, lack of motivation, and loss of empathy (25). Cognitive symptoms in RS were initially described as 'subcortical dementia' characterized by bradyphrenia and executive dysfunction based on involvement of the frontal-subcortical circuit (1). Recent studies of cognitive impairment in RS have further suggested impairment in executive function with milder difficulties in memory, construction, and naming (26), although this study does not have pathological confirmation of a PSP diagnosis.

Hassan et al. reviewed the medical records of 66 autopsy-proven PSP cases between 1973 and 2010 and described three patients with insidious marked changes in personality and behavior with onset of symptoms in their 6th decade. Two of these patients carried a clinical diagnosis of bvFTD during their lifetime. All patients had no parkinsonian manifestations

described in their records until 3–7 years after onset of symptoms. In addition, these patients had progressive loss of social and personal conduct as well as early emotional blunting and loss of insight throughout their disease course (27). Thus, these three cases had a phenotypic presentation of PSP-bvFTD.

Kertesz et al. (24) described a 63-year-old female with onset of disinhibition, personality changes, impulsive behavior, and apathy at the age of 59 who had pathological changes consistent with PSP. Falling off her bicycle and stiff and unsteady gait that appeared approximately 3 years after the onset of her behavioral problems characterized her movement disorder symptoms. She belonged to a family with autosomal-dominant FTD with Tar DNA-binding protein-43 (TDP-43) pathology, although she had no mutations in FTD-associated genes.

PSP–primary lateral sclerosis (PSP-PLS)

Primary lateral sclerosis is a symmetrical disease process affecting upper motor neurons with degeneration of the corticospinal tracts. Clinically, patients present with insidious onset of a symmetric, slowly progressive spastic paresis in adults, which begins in the lower extremities but eventually involves all four extremities and marked pseudobulbar features (28). Its pathology is ordinarily distinct from that found in PSP, showing neuronal loss in the precentral gyrus with corticospinal tract degeneration, but with preservation of lower motor neurons.

Josephs et al. described 12 cases with pathological features that overlapped those of PSP but also with prominent corticospinal tract degeneration similar to PLS. Cortical atrophy of the precentral gyrus and the corticospinal tract with neuronal loss and gliosis in the motor cortex was seen in all cases. The authors reported less tau pathology in the basal ganglia and brainstem nuclei than in cases with typical pathological PSP findings. Most patients in their cohort had prominent parkinsonian manifestations as well as pyramidal tract signs, clinically (29). According to the authors, none of the patients met clinical diagnostic criteria for PSP.

Nagao et al. reported an autopsy-confirmed case of PSP with a clinical presentation of progressive upper motor neuron signs consistent with a clinical diagnosis of PLS. This patient presented with speech difficulty, followed by gait and swallowing difficulties. Hyperreflexia and spasticity, predominantly in the lower extremities, were present. The clinical presentation lacked any typical symptoms associated with PSP, including parkinsonism, vertical gaze palsy, or early falls throughout her clinical course. This case met pathological criteria for PSP including tufted astrocytes, NFTs, coiled bodies, and thread-like structures without TDP-43 accumulation, fused in sarcoma (FUS) pathology, Bunina body, or Lewy body-like hyaline inclusions in the frontal cortex or lower motor neurons. In addition, the authors described argyrophillic and tau-positive neuronal and glial inclusions in the motor cortex and, to a lesser degree, in the basal ganglia and brainstem nuclei, consistent with pathological changes observed in PSP (30). The authors suggested classifying this case as cortical predominant atypical PSP.

King et al. (31) reported a similar case of a patient presenting as primary lateral sclerosis but with pathological evidence of PSP and no obvious abnormality of the motor cortex.

PSP–pallido-nigro-luysian degeneration and axonal atrophy (PSP-PNLA)

Pallido-nigro-luysian-atrophy is a neurodegenerative disease due to bilateral degeneration of the globus pallidus, substantia nigra, and the subthalamic nucleus of Luys with significant clinical heterogeneity. Ahmed et al. (32) identified eight cases with pathology consistent with PNLA out of 400 pathologically confirmed cases of PSP. Because all cases met clinical and pathological criteria for PSP, they called these cases PSP-PNLA and recommended inclusion of PSP-PNLA as a PSP variant. The authors described specific regional pathological tau-related changes in patients with PSP-PNLA with severe degeneration and axonal dystrophy in a pallido-nigro-luysial distribution. In general, patients with PSP had a greater tau burden than those with PSP-PNLA. The major differences in the clinical presentation between patients with PSP and PSP-PNLA pathology were not the presence or absence of a particular clinical feature but rather the timing of occurrence. PSP-PNLA patients had earlier gait abnormalities and difficulty with handwriting followed by freezing of gait. Falls had a much later appearance in the disease course and were not an initial presentation. Patients with PSP but without PNLA pathological findings had a more classic presentation of RS.

Rare phenomenology associated with PSP pathology

Multiple system atrophy (MSA)

Koga et al. recently published a study of 134 autopsy cases with a clinical diagnosis of MSA where only 83 (62%) cases met confirmatory pathological criteria. The remaining 51 cases met pathological criteria for Dementia with Lewy Bodies, PSP, and Parkinson disease (19). Twenty-nine percent (15/51) of misdiagnosed cases met pathological criteria for PSP. Diagnostic accuracy for MSA was not different between general neurologists and movement disorders specialists. After retrospective chart evaluation, the authors found that the most frequent reason for misdiagnosing PSP as MSA was the presence of cerebellar ataxia. The authors suggest that a diagnosis of PSP should be included in the differential diagnosis of patients with cerebellar ataxia and features of atypical parkinsonism.

Normal pressure hydrocephalus

A study by Magdalinou et al. described four patients with an initial diagnosis of idiopathic normal pressure hydrocephalus (iNPH). These patients' clinical course had progressive deterioration and a revision of the clinical diagnosis to PSP was performed 2–4 years after the initial iNPH diagnosis. All patients had a transient response to large volume CSF drainage or ventroperitoneal shunt (VP) placement. The final clinical diagnosis of PSP at autopsy was confirmed in three of the four patients. One patient received a diagnosis of PD (33). Even though the clinical diagnosis became evident over time, it is worth mentioning that careful monitoring and appropriate investigative studies need to be considered when evaluating patients presenting with abnormal MRI findings suggestive of iNPH. The authors

hightlight that recurrent falls in patients with PSP can cause head injuries that could result in secondary NPH.

Essential tremor (ET)

In 2008, Shill et al. (34) described the histopathological findings of 24 subjects with ET followed prospectively, where four were found to have incidental tauopathies at autopsy, including one who met pathological criteria for PSP. Patients with parkinsonism, movement disorders, and/or dementia were not included in their cohort. More recently, Louis et al. recently reported 11 (12.4%) of 89 patients with a clinical diagnosis of ET who received a postmortem diagnosis of PSP. These cases were prospectively collected at the Essential Tremor Centralized Brain Repository (ETCBR) during the course of 9 years. The median duration of ET symptoms was 38 years with 5–49 years latency from onset of ET to development of parkinsonism or dementia. In addition, 8 of the 11 patients had one or more relatives with a diagnosis of ET (35). The onset of parkinsonism in this cohort of patients was age 70s and 80s. Moreover, the *MAPT* H1 haplotype, a genetic risk factor for PSP, has been suggested as a risk factor for ET (36). In contrast, Rajput et al. (37) reported two cases with with ET and pathological findings consistent with PSP. However, given the duration of tremor and the onset of PSP clinical features, the authors concluded that there was no association between ET and PSP pathology. No other studies have confirmed an association between PSP pathology and ET.

Guadeloupean PSP-like syndrome

In 1999, Caparros-Lefebvre et al. (38) described an abnormally high frequency of atypical parkinsonism in the French Caribbean island of Guadeloupe thought to be linked to consumption of herbal tea and fruits from the Annonaceae family, suggesting a possible link to the neurotoxic benzyltetrahydroisoquinoline alkaloids, a known mitochondrial complex 1 inhibitor. Although not all patients showed the same clinical phenotype, there was a subset of patients who showed atypical parkinsonism with predominant axial rigidity, symmetrical bradykinesia, characteristic cognitive decline of frontal lobe function, negligible or at best transient postural instability with early falls, and poor response to dopaminergic therapy. Histopathological data were later found to be consistent with PSP in a large portion of these patients (39).

Treatment of PSP

Currently, there are no effective neuroprotective or disease altering treatments available for patients with PSP. However, some treatment strategies have been reported in the literature and are intended to improve specific symptoms. These strategies could be considered when dealing with these patients in the clinical setting.

Treatment with levodopa, especially in patients with a more parkinsonian phenotype, should be considered because some individuals may show a mild–to-moderate response for a period of time (9, 40). Use of other dopaminergic agents can be found in the literature with very limited efficacy (40). However, cautious monitoring of side effects need to be balanced against potential benefit in this patient population (40). Rajput et al. (41) described the motor

response to amantadine in 14 patients with PSP and reported some improvement in bradykinesia, rigidity, and daily life function. Golbe has also discussed the limited efficacy of amantadine treatment in these patients (42). Careful upward titration with a defined treatment period and evaluation of efficacy are important to avoid unnecessary side effects and prompt discontinuation, if not effective (40). Botulinum toxin can be considered to treat blepharospasms and other dystonic manifestations (43). The need for supportive treatment for dysphagia and fall prevention with speech therapy, physical therapy, and occupational therapy should be periodically assessed in patients and discussed with their caregivers. Other symptoms such as depression, agitation, and other non-motor symptoms need to be addressed on a case-by-case basis with available therapies for the specific symptom. Avoidance of dopamine blocking agents is critically important. A number of potentially neuroprotective modalities including glycogen synthase kinase 3 inhibitors (GSK-3), microtubule stabilization agents, and mitochondrial nutrients such as coenzyme Q10 are currently under investigation (44).

Discussion

Difficulties in the diagnosis of PSP are likely multifactorial. Available diagnostic criteria may be useful for research purposes but when applied to clinical practice may be insufficiently sensitive. Supranuclear ophthalmoplegia can be seen in several disorders and requirement of symptoms to be present within a specific time frame may exclude many pathologically confirmed cases. The presence of clinical signs and symptoms not included in the initial description also affects diagnostic accuracy. It is possible that disease duration at the time of presentation likely affects the clinical features apparent in ‘early’ stages of the disease compared to later stages, further complicating the interpretation of clinical and/or pathological findings.

It is reasonable to assume that different phenomenology is due to differences in anatomical distribution of tau pathology, density of tau concentration in the specific affected areas, and possibly specific tau structural changes contributing to morphological and/or functional changes in synaptic and neuronal structures. In addition, individual genetic, epigenetic, and environmental factors may be influencing disease onset and/or disease progression.

The incidence and natural history of the non-RS phenotypes are largely unknown because large multicenter clinicopathological studies are missing and most series reported to date have been derived from single centers with unavoidable recruitment bias. Lack of standardized clinical evaluation and documentation further complicates our ability to understand phenomenology and disease progression as evident in the fact that retrospective review of medical records in clinicopathological studies use different criteria for the inclusion or exclusion of symptoms associated with disease because they are based on written documentation. Timing of symptom documentation is strongly dependent on interviewer skills, level of suspicion for a specific diagnosis, and awareness of specific symptoms by caregivers.

The classification of disease is getting rather complicated these days as knowledge accumulates. Limitations of the current clinical classification for PSP phenomenology are

complex. The lack of biomarkers to differentiate parkinsonian syndromes early in the disease coursein combination with the lack of standardized evaluation of patients in multicenter studies result in inadequately powered studies to draw generalizable conclusions. Dependence on brain banks for pathologically confirmed PSP cases skews results toward more challenging or ambiguous clinical presentations. Retrospective chart reviews of pathological cases may not contain adequate detailed information about all symptoms or symptom onset to provide an accurate representation of clinical phenomenology. The use of diverse pathological staining methods may contribute to divergent diagnostic conclusions. In addition, pathological findings interpretation is heavily dependent on disease stage at the time of death contributing to varying clinical features and associated pathological findings. Lu et al. (45) recently described different possible genetic mechanisms that make prediction of clinical and treatment prognosis challenging.

Advances in genetic, neuroimaging, and biochemical/molecular technologies will continue to increase our ability to differentiate and identify clinical phenotypes. Prospective multidisciplinary clinical research focusing on understanding subtle differences in signs and symptoms combined with further verification with neuroimaging, pathology, biochemistry, and genetic studies will certainly continue to expand the possible subtypes and different clinical presentations as well as minimize misdiagnosis. This multidisciplinary approach will very likely contribute to the discovery of specific pathophysiological mechanisms, to the identification of biomarkers that can be used to assess disease progression and measure response to the therapies, and to the development of disease modifying therapies.

Conclusion

This review reflects the spectrum of different PSP phenomenologies associated with PSP confirmatory pathological criteria. These differences could be due to differences in topographical distribution of tau pathology and/or differences in the density of tau deposition in the specific affected areas. In addition, morphological and/or functional changes in synaptic and neuronal structures in the early or later stages of PSP are likely contributors to phenotypic expression. Thus, knowledge of the classic RS presentation and of atypical subtypes of PSP can help clinicians with earlier recognition and treatment choices when dealing with these patients. It can also provide more accurate prognosis for patients and their families so that more realistic expectations and future outcomes can be reached.

Prospective multidisciplinary standardized clinical research focusing on understanding subtle differences in signs and symptoms combined with further verification with advanced biotechnological methods will certainly minimize possible misdiagnosis and expand possible additional phenomenologies in the future.

Acknowledgements

The authors declare that this manuscript has not been published before and is not currently being considered for publication elsewhere.

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