

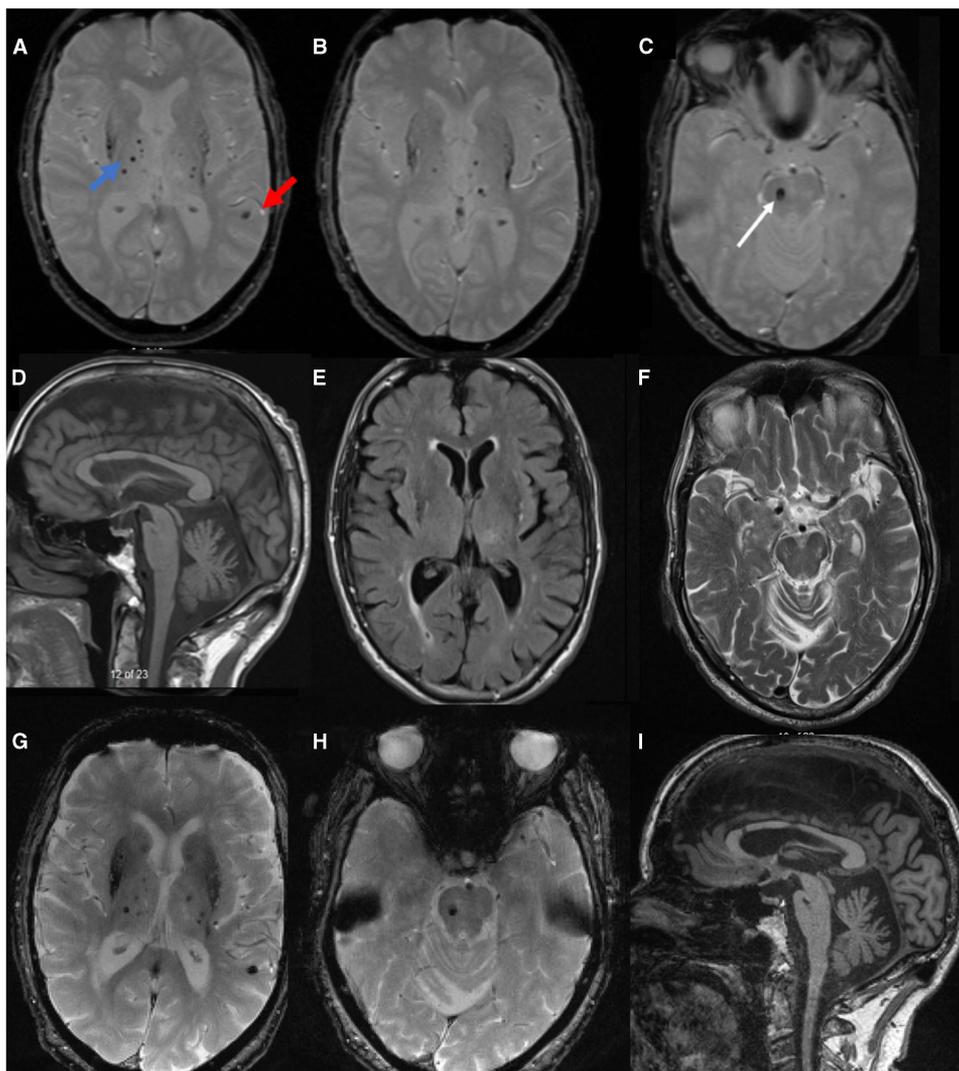
**LETTER TO THE EDITOR****TO THE EDITOR****Progressive Supranuclear Palsy-like Syndrome from Possible Cerebral Amyloid Angiopathy**

**Keywords:** Parkinsonism, Progressive supranuclear palsy, Cerebral amyloid angiopathy

Progressive supranuclear palsy (PSP) is an atypical parkinsonian syndrome comprising of supranuclear vertical gaze palsy, pseudobulbar affect, postural instability, along with cognitive

decline. Progressive supranuclear palsy is a neurodegenerative tauopathy. However, there are several conditions that can clinically mimic PSP presentation. New diagnostic criteria were developed by the International Parkinson and Movement Disorders Society (MDS)<sup>1</sup> to improve the sensitivity and specificity for diagnosis of PSP/PSP variants. We report a case of an atypical PSP and emphasize the approach to PSP and other PSP-like presentations.

A 75-year-old right-handed male presented with a 5-year-history of slow progressive parkinsonism with gait difficulty and falls in the absence of tremor. He also had slow progressive



**Figure 1:** MRI brain

(A and B): axial gradient echo demonstrating multiple areas of signal drop out best seen as blooming in the cortical (red arrow) and subcortical region involving bilateral putamen (blue arrow) and surrounding subcortical structures, including thalami suggestive of multiple bleeds; (C): at the level of pons, the white arrow points to an area of signal drop out at the right pons, suggestive of right pontine bleed. This correlates with the clinical finding of right gaze restriction. The structure of the dorsal midbrain, basal ganglia and thalamus are shown in D, E and F. The ratio of midbrain to pons in TIW mid-sagittal section is 0.69, which argue against PSP (D).<sup>2</sup> Axial midbrain T2 sequence showed no atrophy, and dorsal midbrain is measured at 10 mm. With repeat MRI 5 years later (G-I), no significant worsening was seen on the T2\* sequence at the level of pons and basal ganglia when compared with the initial MRI. There is no progressive dorsal midbrain atrophy (I). However, progressive cerebral atrophy was seen. PSP = progressive supranuclear palsy.

**Table 1: List of the differential diagnoses of abnormal eye movements with postural instability and Parkinsonism [modified and updated from Williams and Lees<sup>13</sup>]**

Clinical diagnosis	Cardinal features
PSP	Axial > appendicular rigidity, supranuclear vertical gaze palsy, early postural instability and falls MRI brain: <ul style="list-style-type: none"> <li>• Midbrain:pons ratio &lt;0.52<sup>2</sup></li> <li>• Midbrain measurement &lt;9.35 mm</li> <li>• Hummingbird sign</li> <li>• Morning glory sign</li> </ul>
CBGD	Asymmetrical akinetic rigidity syndrome, with cortical signs (cortical sensory loss, apraxia and alien limb phenomenon) and extrapyramidal signs (rigidity, dystonia and myoclonus) MRI brain: <ul style="list-style-type: none"> <li>• Asymmetrical perirolandic cortical atrophy</li> <li>• Bilateral atrophy of basal ganglia</li> <li>• Signal change in frontal/parietal subcortical white matter</li> <li>• Asymmetry with cerebral peduncle</li> </ul>
CBS	Asymmetrical akinetic rigidity syndrome, also see above. CBS is frequently PSP in pathology, rarely CBGD <sup>14</sup> MRI brain: <ul style="list-style-type: none"> <li>• Asymmetrical perirolandic cortical atrophy</li> <li>• Bilateral atrophy of basal ganglia</li> <li>• Atrophy of corpus callosum</li> </ul>
MSA	Autonomic dysfunction and ataxia. Vertical gaze palsy is uncommon. May have cerebellar eye findings MRI brain: <ul style="list-style-type: none"> <li>• MSA-C: <ul style="list-style-type: none"> <li>• Hot cross bun sign</li> <li>• Pons, cerebellum and inferior olives atrophy</li> </ul> </li> <li>• MSA-P: <ul style="list-style-type: none"> <li>• Reduced volume of putamen, and decrease T2 signal in dorsolateral putamen</li> <li>• Putamen rim sign on T1 and GRE</li> </ul> </li> </ul>
FTD associated with chromosome 17	Personality and behavioral abnormalities. Language deficit may exist. Early abnormalities with anti-saccade MRI brain: <ul style="list-style-type: none"> <li>• Frontal and temporal lobe atrophy</li> <li>• Reduced size of the caudate in behavioral variant of FTD</li> </ul>
MND	Both upper and lower motor neuron signs on examination. Parkinsonism may co-exist. The associated eye movement abnormalities consistent with supranuclear gaze palsy are usually associated with the bulbar variant of MND
Niemann Pick type C	Most present in the second or third decade. Associated signs are cerebellar ataxia, dysarthria, dysphagia, psychiatric symptoms, cognitive dysfunction and vertical supranuclear gaze palsy Genetic studies: NPC1/NP2 gene Filipin test on cultured fibroblasts
Prion disease	Patients presenting with supranuclear gaze paresis, parkinsonism and poor postural responses has been described especially with genetic forms of prion disease MRI brain: <ul style="list-style-type: none"> <li>• T2 weighted hyperintensities in basal ganglia and thalamus (hockey-stick and pulvinar sign)</li> <li>• Cortical ribboning</li> <li>• DWI/ADC: persistent restriction</li> <li>• CSF: 14-3-3, RT-QuIC</li> </ul>
SCA type 2, 3 and 17	SCA2: ataxia ± parkinsonism with decreased horizontal saccadic velocity and hypometric saccades. Late stages can have total ophthalmoparesis SCA3: ataxia ± parkinsonism with hypometric dysmetria and square wave jerks SCA17: ataxia, behavioral abnormalities, parkinsonism along with smooth pursuit abnormalities and hypometric saccades
Whipple's disease	Eye findings mimic PSP. It is characterized by cognitive impairment, parkinsonism, vertical saccade slowing along with up gaze restriction and oculomasticatory myorhythmia CSF: PCR for <i>Tropheryma whipplei</i>
Cerebral vascular disease	Multi-infarct state: patients can have step wise progression with asymmetrical signs on examination. Eye findings vary due to locations of the lesion(s) CAA: clinical and MRI findings are characterized by: <ul style="list-style-type: none"> <li>• Cerebral lobar hemorrhage</li> <li>• Corticosubcortical microhemorrhages</li> <li>• Convexal subarachnoid haemorrhage</li> <li>• Cortical superficial siderosis</li> <li>• Ischemic leukoencephalopathy</li> </ul> CADASIL: clinically present with migraine, early onset of stroke and dementia MRI brain: <ul style="list-style-type: none"> <li>• Confluent white matter hyperintensities</li> <li>• Circumsized hyperintensities seen in pons and thalamus</li> <li>• Relative sparing of "U" fibers at occipital and orbitofrontal subcortical white matter</li> <li>• Notch 3 gene for CADASIL if indicated</li> </ul>

**Table 1:** *Continued*

Clinical diagnosis	Cardinal features
Neurosyphilis	Very rarely secondary syphilis can be associated with vertical gaze paresis. Parkinsonism although rare has been reported with neurosyphilis CSF:VDRL and TPHA
IgLON5 encephalitis	Patients develop a characteristic sleep disorder preceded or accompanied by bulbar symptoms, gait abnormalities, oculomotor problems and cognitive decline. Rapid progressive course MRI can be normal Serum and CSF IgLON5 antibodies, IgG4 subclass predominate over IgG1 A strong association with the HLA-DRB1*10:01 allele <sup>15</sup>

ADC = apparent diffusion coefficient; CAA = cerebral amyloid angiopathy; CADASIL = cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy; CBGD = corticobasal degeneration; CBS = corticobasal syndrome; DWI = diffusion weighted imaging; FTD = frontotemporal degeneration; GRE = gradient echo; MND = motor neuron disease; MSA = multiple system atrophy; MSA-C = multiple system atrophy with cerebellar features; MSA-P = multiple system atrophy with parkinsonism; NPC1/NPC2 = NPC intracellular cholesterol transporter 1 = NPC = intracellular cholesterol transporter 2; PCR = polymerase chain reaction; PSP = progressive supranuclear palsy; SCA = spinocerebellar ataxia; TPHA = treponema pallidum haemagglutination test; VDRL = the venereal disease research laboratory.

cognitive decline over the course of 3 years with impaired episodic memory and executive function. He did not have urinary incontinence or behavioral changes. He took 1000 mg of levodopa daily for 2 years with poor response. He did not report dyskinesia.

Examination showed normal blood pressure and pulse (120/76 mmHg and 88 per minute, supine) with no postural changes (120/72 mmHg and heart rate 92 per minute, standing). He scored 19/30 on the Montreal Cognitive Assessment, with difficulties in visuospatial tasks, attention, verbal fluency and delayed recall (improved with categorical cues). He had ideomotor apraxia with impaired spatiotemporal aspects of movements, but did not have any cortical sensory loss or alien limb phenomenon. He had restricted vertical gaze and horizontal gaze to the right only, saccadic pursuits, and impaired saccadic initiation and velocity in the absence of square wave jerks. His gaze restrictions were overcome by the vestibulo-ocular reflex. On optokinetic nystagmus (OKN) testing, there was preserved corrective nystagmus to the right when the OKN strip moved to the left, but OKN was impaired when the OKN strip moved to the right and vertically. He was dysarthric with palilalia (online Supplementary Video 1). He had axial and appendicular rigidity (left > right). Power was intact. There was bradykinesia with finger tapping and rapid alternating movements, with frequent arrests of movements. There was subtle asymmetry with deep tendon reflex (DTR). It was easier to elicit his DTRs at the right side, but they were still 2+. He had flexor plantar response bilaterally. There were no other pyramidal findings. There were no frontal release signs on examination. Applause sign was negative. Gait was slow with decreased stride length and reduced arm swing bilaterally. He had poor postural reflexes on pull testing (online Supplementary Video 1). Through the course of follow-up, his parkinsonism and balance progressed, along with his cognitive function. However, the extraocular movements did not evolve from the initial examination.

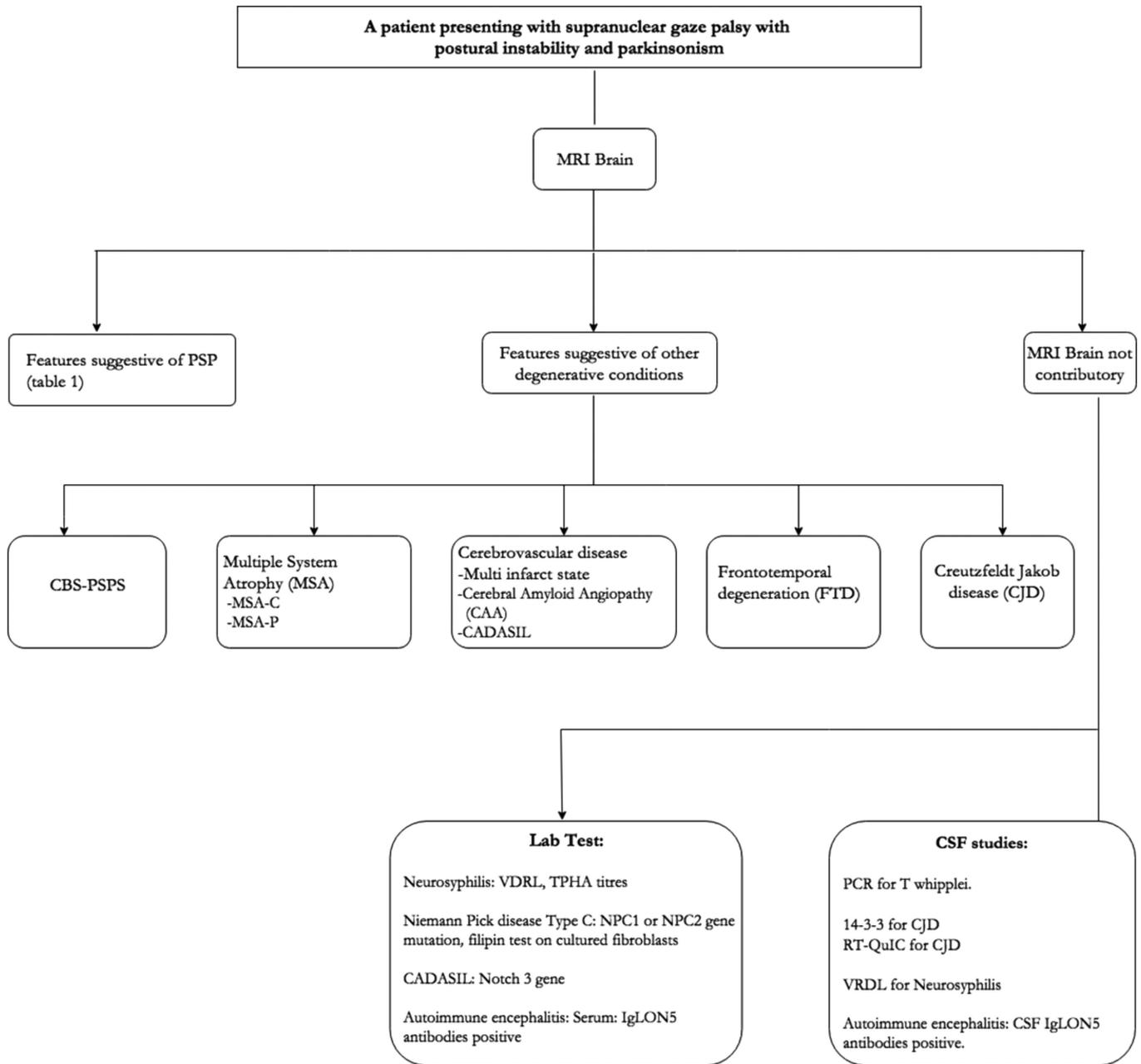
Restricted vertical gaze, with asymmetrical restriction with horizontal gaze (only to the right) is not characteristic of degenerative taopathies. The brain MRI performed 2 years from onset of symptoms demonstrated multiple cortical bleeds, and a right pontine bleed, which explained his asymmetrical horizontal gaze restriction. Basal ganglia microbleeds were also evident (Figure 1). There were multiple ischemic changes in the midbrain

and frontal white matter bilaterally. These changes can be seen in association with hypertension, aging and cerebral amyloid angiopathy (CAA). This case is atypical for degenerative PSP given the normal midbrain size and midbrain to pons ratio (Figure 1)<sup>2</sup> and the other atypical clinical and radiological findings. A repeat MRI 5 years after the initial scan showed progressive brain atrophy. Midbrain measurement and midbrain to pons ratio remained normal. Such findings argue against PSP. There was an increase in microbleeds in the subcortical regions, which might explain the slow cognitive decline.

Conditions like multiple system atrophy (MSA),<sup>3</sup> dementia with lewy bodies (DLB),<sup>4</sup> Alzheimer's disease, motor neuron disease and vascular etiologies can present with parkinsonism, supranuclear gaze palsy and postural instability. Based on the MDS PSP diagnostic criteria,<sup>1</sup> the exclusion criteria require these conditions to be ruled out on history, clinical examination or imaging. While MSA or DLB are to be chiefly excluded on clinical grounds, the criteria also lay out several conditions that need to be excluded based on their characteristic MRI findings. These include severe leukoencephalopathy, relevant structural abnormalities, vascular parkinsonism along with its associated syndromes (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy and CAA) and prion disease.

Among the PSP mimics, DLB, spinocerebellar ataxias, MSA and frontotemporal dementia with chromosome 17 mutations can exhibit parkinsonism, postural instability and supranuclear gaze palsy (Table 1). Our patient did not have visual hallucinations, fluctuating sensorium, rapid eye movement sleep behavioral disorder, autonomic dysfunction, ataxia or behavioral issues making the above diagnoses unlikely. He had no clinical history evidence for ischemic stroke, making typical vascular parkinsonism unlikely. He did not have oculomasticatory myorhythmia, although he had ocular findings that could still suggest Whipple disease; however, the MRI findings suggested an alternative diagnosis.

The most common etiology for the cerebral microbleeds is CAA, which is classically associated with cortical bleeds. Sveinbjornsdottir et al<sup>5</sup> and Fisher et al<sup>6</sup> reported that microhemorrhages were found in non-hypertensive subjects with no prior history of stroke, and concluded that microbleeds can occur in an aging brain with the most common site being the putamen



**Figure 2:** Flowchart for approach to a patient with parkinsonism, supranuclear gaze palsy and postural instability.

PSP = progressive supranuclear palsy; CBS-PSPS = corticobasal syndrome-progressive supranuclear palsy syndrome; MSA = multiple system atrophy; MSA-C = multiple system atrophy with cerebellar features; MSA-P = multiple system atrophy with parkinsonism; CAA = cerebral amyloid angiopathy; CADASIL = cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy; FTD = frontotemporal degeneration; CJD = Creutzfeldt–Jakob disease; VDRL = venereal disease research laboratory; TPHA = treponema pallidum haemagglutination test; NPC1/NPC2 = NPC intracellular cholesterol transporter 1/NPC intracellular cholesterol transporter 2; PCR = polymerase chain reaction.

irrespective of hypertension status. The most common pathology found in these patients was CAA, while atherosclerosis with fibrinohyalinosis or co-existing dual pathologies are less common.

Cerebral amyloid angiopathy is a heterogeneous disorder with amyloid deposition in the small to medium sized leptomeningeal and cortical arterioles. Clinically, CAA associated vasculopathy is characterized by lobar cerebral hemorrhages, cortical micro-

hemorrhages, superficial siderosis, subarachnoid hemorrhage and cortical infarcts with ischemic white matter changes. Very rarely, it can present with an encephalopathy in CAA related angiitis.<sup>7</sup> Interestingly, some pathological studies have shown a higher incidence of CAA deposition in idiopathic Parkinson's disease (53% vs. 24% in control), more pronounced in patients with DLB and Parkinson dementia complex.<sup>8</sup> A multi-infarct state may also present with a PSP spectrum presentation (CT, MRI brain or autopsy).<sup>9</sup>

This case presents an atypical PSP-like syndrome with cerebral microbleeds secondary to CAA being the most likely etiology. To date, only one previous series demonstrated a single patient with pathological evidence of CAA. The reported case had vascular lesions secondary to CAA in the right centrum semiovale, substantia nigra, diencephalon and pons.<sup>9</sup> Another case series by Josephs et al<sup>10</sup> demonstrated four pathological cases with vascular lesions presenting as PSP-like syndrome in the absence of tauopathy. The patients may have asymmetrical neurological signs such as cranial nerve VII palsy, hemiparesis, the Babinski sign or leg dystonia which could serve as clinical clues to differentiate from PSP. Interestingly, all subjects had frontal infarcts, three had unilateral basal ganglia and right thalamic infarcts, while bilateral thalamic infarcts were seen in one patient. Similarly, only one patient had infarcts in the basis pontis and medullary tegmentum. In our patient with multiple microbleeds, while CAA or atherosclerosis with fibrinohyalinosis is the likely pathology, whether he has co-existing dual pathologies remains unproven without tissue diagnosis or tau imaging.

Classically, structural lesions involving the rostral interstitial nucleus of the medial longitudinal fasciculus, the interstitial nucleus of Cajal, and the posterior commissure will cause vertical gaze palsy, but that was not the case with our patient. Supranuclear vertical gaze palsy, in our case, may be secondary to the midbrain stroke or disruption by the thalamomesencephalic lesions, both of which have been described previously to cause vertical gaze restrictions.<sup>11,12</sup> Similarly, the parkinsonism and poor postural balance are likely secondary to the disruption of the cortico-pallidal-nigro-thalamo-cortical loops.

Although a co-associated tauopathy cannot be ruled out, it remains imperative to exclude PSP mimics by following the MDS diagnostic criteria before designating PSP as the final diagnosis. Many of these PSP-mimics, such as Niemann Pick type C, neurosyphilis, IgLON5 encephalitis and whipple disease may be treatable and carry different prognosis than PSP itself. Careful history and examination with appropriate neuroimaging (Figure 2), including gradient echo or susceptibility weighted imaging, are required before making the diagnosis of PSP.

#### FUNDING SOURCES

There are no funding sources for this case report. Repeat imaging was performed as part of the Function Assessment of Vascular Reactivity Study (Eric E. Smith, PI, University of Calgary, Richard Camicioli, site-principal investigator, University of Alberta, funded by Brain Canada and Canadian Institutes of Health Research).

#### AUTHORS' CONTRIBUTIONS

AS participated in patient evaluation, drafting/revising the manuscript and acquisition of data. RC participated in study concept and critical revision of the manuscript. FB participated in study concept, acquisition of data and critical revision of the manuscript.

#### CONFLICTS OF INTEREST/FINANCIAL DISCLOSURES

The authors declare that they have no competing interests. The authors report no financial disclosures. FB, AS and RC have nothing to disclose.

#### SUPPLEMENTARY MATERIAL

To view supplementary material for this article, please visit <https://doi.org/10.1017/cjn.2018.367>

*Aakash Shetty*

*Division of Neurology, Department of Medicine, University of Alberta, Edmonton, Alberta, Canada*

*Richard Camicioli*

*Division of Neurology, Department of Medicine, University of Alberta, Edmonton, Alberta, Canada*

*Fang Ba*

*Division of Neurology, Department of Medicine, University of Alberta, Edmonton, Alberta, Canada*

*Correspondence to:* Fang Ba, Division of Neurology, Department of Medicine, University of Alberta, 7-112 Clinical Sciences Building, 11350-83 Avenue, Edmonton, Alberta, Canada T6G 2G3. Email: fb@ualberta.ca

#### REFERENCES

- Hoglinger GU, Respondek G, Stamelou M, et al. Clinical diagnosis of progressive supranuclear palsy: the movement disorder society criteria. *Mov Disord.* 2017;32(6):853-64.
- Massey LA, Jager HR, Paviour DC, et al. The midbrain to pons ratio: a simple and specific MRI sign of progressive supranuclear palsy. *Neurology.* 2013;80(20):1856-61.
- Anderson T, Luxon L, Quinn N, Daniel S, David Marsden C, Bronstein A. Oculomotor function in multiple system atrophy: clinical and laboratory features in 30 patients. *Mov Disord.* 2008;23(7):977-84.
- Clerici F, Ratti PL, Pomati S, et al. Dementia with Lewy bodies with supranuclear gaze palsy: a matter of diagnosis. *Neurol Sci.* 2005;26(5):358-61.
- Sveinbjornsdottir S, Sigurdsson S, Aspelund T, et al. Cerebral microbleeds in the population based AGES-Reykjavik study: prevalence and location. *J Neurol Neurosurg Psychiatry.* 2008;79(9):1002-06.
- Fisher M, French S, Ji P, Kim RC. Cerebral microbleeds in the elderly: a pathological analysis. *Stroke.* 2010;41(12):2782-85.
- Biffi A, Greenberg SM. Cerebral amyloid angiopathy: a systematic review. *J Clin Neurol.* 2011;7(1):1-9.
- Jellinger KA, Attems J. Cerebral amyloid angiopathy in Lewy body disease. *J Neural Transm (Vienna).* 2008;115(3):473-82.
- Dubinsky RM, Jankovic J. Progressive supranuclear palsy and a multi-infarct state. *Neurology.* 1987;37(4):570-76.
- Josephs KA, Ishizawa T, Tsuboi Y, Cookson N, Dickson DW. A clinicopathological study of vascular progressive supranuclear palsy: a multi-infarct disorder presenting as progressive supranuclear palsy. *Arch Neurol.* 2002;59(10):1597-601.
- Iijima M, Hirata A, Tadano Y, Kamakura K, Nagata N. A case of vertical gaze palsy associated with a unilateral infarct in the thalamo-mesencephalic junction on MR imaging. *Rinsho Shinkeigaku.* 1994;34(4):356-60.
- Clark JM, Albers GW. Vertical gaze palsies from medial thalamic infarctions without midbrain involvement. *Stroke.* 1995;26(8):1467-70.
- Williams DR, Lees AJ. Progressive supranuclear palsy: clinicopathological concepts and diagnostic challenges. *Lancet Neurol.* 2009;8(3):270-79.
- Armstrong MJ, Litvan I, Lang AE, et al. Criteria for the diagnosis of corticobasal degeneration. *Neurology.* 2013;80(5):496-503.
- Gaig C, Graus F, Compta Y, et al. Clinical manifestations of the anti-IgLON5 disease. *Neurology.* 2017;88(18):1736-43.