A Clinicopathological Study of Vascular Progressive Supranuclear Palsy

A Multi-infarct Disorder Presenting as Progressive Supranuclear Palsy

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**Background:** Clinical features suggesting a diagnosis of progressive supranuclear palsy (PSP) include early falls, axial rigidity, vertical supranuclear ophthalmoplegia, and levodopa unresponsiveness. When these clinical features are present, the diagnosis is almost always PSP, yet vascular disease sometimes has a similar presentation, referred to as vascular PSP.

**Objective:** To evaluate clinical and pathologic features of cases of vascular PSP submitted to a PSP brain bank.

**Design:** Review of gross and microscopic neuropathological features, determination of \( H^2 \) haplotype, and medical record review of 4 patients with an antemortem diagnosis of PSP who did not meet the pathologic criteria for PSP and instead had vascular pathologic abnormalities.

**Results:** All patients had vertical supranuclear ophthalmoplegia, a history of falls, and a gradually progressive disease course. Falls began 1 year after symptom onset, and all patients had asymmetric findings on a neurological examination. A magnetic resonance imaging scan revealed lacunar basal ganglia infarcts in one patient and an increased T2-weighted signal in the corona radiata and centrum semiovale in another. Gross and microscopic neuropathological studies demonstrated infarcts in the cerebral cortex (n=4), thalamus (n=4), basal ganglia (n=3), and cerebellum (n=4). The brainstem was affected in one patient, but no infarcts were detected in the subthalamic nucleus or substantia nigra. Of the 4 patients, 3 carried an \( H^2 \) haplotype, a rare occurrence in the general population.

**Conclusions:** Asymmetric signs, falls after 1 year of symptom onset, vascular lesions on a magnetic resonance imaging scan, and an \( H^2 \) haplotype may help differentiate vascular PSP from PSP. Thalamic and basal ganglia infarcts are common in patients with vascular PSP and, when present, may contribute to misdiagnosis.

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STEEL ET AL. first described progressive supranuclear palsy (PSP) in 1964. Since then, several studies have tried to identify features that improve the sensitivity and specificity of clinically diagnosing this entity. Some features that are considered fairly specific to PSP include axial greater than appendicular rigidity, levodopa unresponsiveness, absence of tremor, frontal lobe dysfunction, and symmetric parkinsonism. In 1996, Litvan et al published research criteria for the clinical diagnosis of PSP and defined 3 categories of possible, probable, and definite PSP. The latter was dependent on pathologic confirmation, while the others were based on a combination of clinical features, including onset at age 40 years or older, vertical supranuclear ophthalmoplegia (VSO), early falls, and no evidence of other disorders that could account for the neurological signs. The specificity of the clinical criteria for probable PSP was 100%, decreasing to 89% if exclusion criteria were not met. One of the exclusion criteria was clinical evidence of central nervous system vascular disease.

Progressive supranuclear palsy is a degenerative disorder with neuronal and glial \( \tau \) aggregates in specific cortical and subcortical locations, including the motor cortex, basal ganglia, thalamus, subthalamic nucleus, brainstem, and cerebellum. The clinical phenotype of the \( \tau \)-related diseases is related to the specific anatomical areas of involvement more than the specific biochemical or genetic aspects of the disorder, even though both are believed to be important. In any neurological condition, however, the clinical phenotype is not absolute and, hence, a differential diagnosis is necessary. As early as the 1980s, there were reports of clinically diagnosed PSP with computed tomographic, magnetic resonance imag-
ing, and autopsy evidence of vascular rather than degenerative pathologic abnormalities. The term vascular PSP was coined by Winikates and Jankovic in a report of 30 cases in a clinical series of 128 patients with PSP who satisfied the criteria for vascular PSP. The characteristic features they emphasized for vascular PSP were asymmetric and lower body involvement. Subsequently, Binswanger disease presenting as PSP was described.10

Of all the features considered specific for PSP, the one that carries the most weight is VSO. When present alone, VSO has limited value in differential diagnosis; however, in the right clinical context, it is almost pathognomonic for PSP. Differentiating VSO from vertical nuclear ophthalmoplegia is important when considering a diagnosis of PSP. The latter would suggest structural lesions involving the third and/or fourth cranial nerve nuclei or nerve roots and would not be consistent with PSP. Yet, vascular infarcts resulting in VSO have been described in patients with bilateral lesions11 and even in those with unilateral thalamoencephalitic and rostral interstitial medial longitudinal fasciculus lesions.12–14 Infarcts in the pons, substantia nigra, centrum semiovale, frontal subcortex, striatum, corona radiata, internal capsule, and basal ganglia have been described using magnetic resonance imaging, computed tomography, and an autopsy case of PSP that carried the most weight is VSO. When present alone, VSO has limited value in differential diagnosis; however, in the right clinical context, it is almost pathognomonic for PSP. Differentiating VSO from vertical nuclear ophthalmoplegia is important when considering a diagnosis of PSP. The latter would suggest structural lesions involving the third and/or fourth cranial nerve nuclei or nerve roots and would not be consistent with PSP. Yet, vascular infarcts resulting in VSO have been described in patients with bilateral lesions and even in those with unilateral thalamoencephalitic and rostral interstitial medial longitudinal fasciculus lesions. Infarcts in the pons, substantia nigra, centrum semiovale, frontal subcortex, striatum, corona radiata, internal capsule, and basal ganglia have been described using magnetic resonance imaging, computed tomography, and an autopsy case of clinically diagnosed vascular PSP.

In this report, patients with a clinical diagnosis of PSP who failed to meet the pathologic criteria for PSP, but instead had vascular pathologic abnormalities, were assessed to determine if specific lesion patterns could be identified. Only a few autopsy-confirmed cases of vascular PSP have been reported since it was first defined. To our knowledge, this is the largest clinicopathological study of vascular PSP.

### Table 1. Clinical Features of Patients With Vascular PSP Compared With Patients With Pathologically Proved PSP

<table>
<thead>
<tr>
<th>Variable</th>
<th>Patients With Vascular PSP</th>
<th>Patients With Pathologically Proved PSP</th>
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<tbody>
<tr>
<td>Sex/age at death, y</td>
<td>M/87</td>
<td>M or F/78.3†</td>
</tr>
<tr>
<td>Haplootype</td>
<td>H1/H1</td>
<td>H1/H1 in 88%</td>
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<tr>
<td>Disease duration, y</td>
<td>1</td>
<td>12</td>
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<tr>
<td>Falls 1 y after symptom</td>
<td>+</td>
<td>+</td>
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<tr>
<td>onset</td>
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<tr>
<td>Early dysarthria/dysphagia</td>
<td>+</td>
<td>+</td>
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<tr>
<td>Levodopa resistance</td>
<td>NA</td>
<td>+</td>
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<tr>
<td>Axial rigidity</td>
<td>+</td>
<td>+</td>
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<tr>
<td>Other features</td>
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<tr>
<td>HTN</td>
<td>Retrocollis and hypomimia</td>
<td>Hypomimia (stare)</td>
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<tr>
<td>MRI/CT findings</td>
<td>+</td>
<td>+</td>
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<tr>
<td></td>
<td>Increased T2-weighted</td>
<td>Calcium deposits</td>
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<tr>
<td></td>
<td>signal in the corona</td>
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<td></td>
<td>radiates and the centrum</td>
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<td></td>
<td>semiovale</td>
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</table>

* A cognitive change occurred in all patients. PSP indicates progressive supranuclear palsy; +, present; −, absent; L, left; R, right; HTN, history of hypertension; MRI, magnetic resonance imaging; CT, computed tomographic; and NA, data not available.

†Mean.

Two hundred seven cases from the Society for Progressive Supranuclear Palsy brain bank at Mayo Clinic were reviewed for cases that did not meet the pathologic criteria for PSP but had pathologic evidence of vascular disease. All cases underwent a standard neuropathological assessment, including hematoxylin-eosin staining, thioflavine S fluorescent microscopy, and immunostaining with phosphorylated τ monoclonal antibodies (CP13 or PHF1) and a polyclonal antibody to α-synuclein. Fixed and frozen tissues from all cases were dissected and analyzed for gross evidence of large- and small-vessel infarction or hemorrhage. Sections were taken from multiple cortices and the hippocampus, amygdala, basal ganglia, thalamus, mesencephalon,pons, medulla, and cerebellum. The sections were microscopically studied for evidence of infarcts, hemorrhages, and foci of ischemic gliosis. Each case underwent systematic neuropathological assessment, including quantitative analysis of Braak stage, neurofibrillary tangle and senile plaque counts, semiquantitative assessment of amyloid angiopathy, and semiquantitative assessment of τ-related neuronal and glial pathologic features using immunohistochemistry in multiple cortical and subcortical regions. A neurologist (K.A.J.) abstracted the following information from medical records: sex, age of onset, duration of illness, history of hypertension, early vs late falls, early dysarthria or dysphagia, asymmetry, cognitive dysfunction, eye movement abnormalities, parkinsonism, levodopa responsiveness, and imaging findings. Polymerase chain reaction was used to determine τ haplotype from DNA extracted from frozen brain tissue using previously published methods.

Four patients (3 men and 1 woman; mean ± SD age, 79.0 ± 6.3 years) with a clinical diagnosis of PSP satisfied the criteria for vascular PSP (Table 1). Of these 4
patients, 3 had thorough medical records, including documented antemortem imaging studies, for review. All 4 patients had a documented neurological examination by at least one neurologist. The mean age of onset was 73 years, and the mean duration of illness was 6 years. All 4 patients had onset after the age of 40 years, VSO, and a gradually progressive disease course. All 4 patients had a history of falls, but these occurred after 1 year of symptom onset. Axial rigidity, levodopa unresponsiveness, and postural instability. Some unusual features were characterized by VSO, axial rigidity, hypomimia, and postural instability. Some unusual features for the spectrum of PSP included left cranial nerve VII palsies, hemiparesis, the Babinski sign, tremor, rigidity, or leg dystonia. One patient had magnetic resonance imaging evidence of lacunar infarcts in the medulla, and another showed an increased T2-weighted signal in the corona radiata and centrum semiovale.

Pathologic data are summarized in Table 2. On gross examination, all 4 patients had neocortical infarcts in the frontal lobe, and 3 of the 4 had right-sided thalamic infarcts, with bilateral infarcts occurring in 1 (Figure). Three patients also had infarcts in the basal ganglia (Figure). One patient had lacunar infarcts in the pontine base and medullary tegmentum. On microscopic examination, all 4 patients had moderate to marked arteriosclerotic vascular disease, cribriform changes in the basal ganglia, and multiple foci of ischemic gliosis. Pathologic features consistent with PSP were absent in all patients. Age-related Alzheimer disease–type changes were minimal. The mean Braak stage was 2.3 (range, 1-3). Cortical senile plaques were absent, except in patient 2, who had rare senile plaques in the occipital lobe. The subthalamic nucleus was not affected by infarcts or ischemic or hemorrhagic infarcts greater than 1 cm in diameter. The substantia nigra, superior colliculus, periaqueductal gray matter, and cerebellar deep nuclei were free of infarcts and ischemic changes. A microscopic examination in all 4 patients showed small cerebellar infarcts that were not detected on gross inspection. Haplotypic analysis revealed an H2/H2 haplotype in 3 of the 4 patients (2 had the H1/H2 τ genotype and 1 had the H2/H2 τ genotype).

**COMMENT**

This study demonstrated that vascular PSP occurs because of multiple vascular lesions, without the cardinal pathologic features of idiopathic PSP. Prominent clinical features of this autopsy-confirmed vascular PSP series were characterized by VSO, axial rigidity, hypomimia, and postural instability. Some unusual features for the spectrum of PSP included left cranial nerve VII palsy in 2 patients and left hemiparesis and the Babinski sign in 1. Other asymmetric features were also seen in all 4 patients. Retrocoliosis and early development of dysarthria or dysphagia, commonly seen in those with PSP, were noted in the patients with vascular PSP. Interestingly, the substantia nigra, subthalamic nuclei, and periaqueductal gray matter, which are prominently affected areas in patients with PSP, were not directly affected in those with vascular PSP. Instead, the right side of the thalamus in 3 patients, the left side of the thalamus in 1 patient, unilateral or bilateral globus pallidus, the puta-

**Table 2. Infarct Distribution in Patients With Vascular PSP Compared With NFT Distribution in Patients With Pathologically Proved PSP**

<table>
<thead>
<tr>
<th>Region</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
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<tr>
<td></td>
<td>R</td>
<td>L</td>
<td>R</td>
<td>L</td>
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<tr>
<td>Frontal lobe</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
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<tr>
<td>Temporal lobe</td>
<td>-</td>
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<td>-</td>
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<tr>
<td>Parietal lobe</td>
<td>+</td>
<td>+</td>
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<td>-</td>
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<tr>
<td>Caudate/putamen</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+</td>
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<tr>
<td>Globus pallidus</td>
<td>-</td>
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<tr>
<td>Basal nucleus</td>
<td>-</td>
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<tr>
<td>Thalamus</td>
<td>+</td>
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<tr>
<td>Subthalamic nucleus</td>
<td>-</td>
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<td>+</td>
<td>+</td>
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<tr>
<td>Red nucleus</td>
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<td>-</td>
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<tr>
<td>Substantia nigra</td>
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<tr>
<td>Oculomotor nerve complex</td>
<td>-</td>
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<tr>
<td>Superior colliculus/periaqueductal gray matter</td>
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<tr>
<td>Locus coeruleus</td>
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<tr>
<td>Pontine tegmentum</td>
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<tr>
<td>Pontine base</td>
<td>-</td>
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<td>+</td>
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<tr>
<td>Medullary tegmentum</td>
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<td>-</td>
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<tr>
<td>Inferior olive</td>
<td>-</td>
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<tr>
<td>Dentate nucleus</td>
<td>-</td>
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<td>-</td>
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<tr>
<td>Cerebellar white matter</td>
<td>-</td>
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<td>-</td>
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<tr>
<td>Cerebellar cortex</td>
<td>+</td>
<td>-</td>
<td>-</td>
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</table>

*PSP indicates progressive supranuclear palsy; NFT, neurofibrillary tangle; R, right; L, left; +, ischemic or hemorrhagic infarcts 1 cm or less in diameter; −, absent; and ++, ischemic or hemorrhagic infarcts greater than 1 cm in diameter.
†Moderate to severe NFT density.
‡Moderate to severe NFT density.
of the lesions in the present series of patients with vas-

cular PSP suggests that thalamic lesions may also pro-
duce VSO, possibly by interrupting supranuclear verti-
cal gaze pathways.

The pathophysiologic conditions of postural in-

stability are poorly understood. It is generally thought
that loss of postural reflex is related to reciprocal con-
nections among the cortex, basal ganglia, and thala-
mus.19,20 A study21 of patients who had experienced a
stroke showed that the parietal-insular cortex or adja-
cent structures, including the basal ganglia, may be cru-
cial in impaired postural balance. Multiple interrup-
tions of the cortical-striatal-pallidal-nigral-thalamic-
cortical loops are most likely responsible for the presence
of parkinsonism in our series. Ischemic or degenerative
destruction of multiple cortical, basal ganglia, and tha-
lamic structures may also be the correlate of the unre-
 sponsiveness to high-dose levodopa therapy in those with
vascular PSP and in those with idiopathic PSP. These
structures depend on numerous neurotransmitters and
are not limited to dopaminergic cell loss.

A diagnosis of PSP was reasonable in these patients

if strict research criteria were not used,3 because all pa-
tients had VSO, parkinsonism, and frequent falls. Fur-

thermore, there was never any apparent episodic dete-
rion in their histories suggestive of isolated or multiple

infarcts. The reason for the lack of these episodes may

have been an absence of apparent plegia, sensory distur-
bances, or focal cortical signs. On the other hand, none

of the patients would have fulfilled the clinical research
criteria proposed by Litvan et al3 for possible or prob-
able PSP because of the late onset of falls, asymmetric

signs, and neuroradiologic abnormalities.3 Winikates and

Jankovic9 suggested that vascular PSP should be differ-

entiated from idiopathic PSP if the patient has a higher
degree of asymmetry, lower body involvement, evi-
dence of corticospinal and pseudobulbar signs, some neu-
romaging evidence of vascular disease, and an in-
creased frequency of risk factors for strokes. Our study
showed that, in addition to asymmetry, frequent falls be-


Macroscopic findings of 3 patients with vascular progressive supranuclear palsy. Arrows indicate grossly apparent hemorrhages or infarcts. A and B, Patient 4 (left hemisphere). There were infarcts in the putamen and thalamus and an old slitlike hemorrhage in the lateral putamen. C, Patient 3 (right hemisphere). There were multiple infarcts in the putamen and globus pallidus and a cortical infarct. D, Patient 2 (left hemisphere). There were multiple infarcts in the putamen and periventricular white matter. Patient 1 is not shown.

men, and the caudate were the main areas involved in

those with vascular PSP.

The vertical gaze control center is known to lie in

mesencephalic reticular formation, which includes the

Darkshevich nucleus, the interstitial nucleus of Cajal, the

rostral interstitial nucleus of the medial longitudinal fasciculus, and the posterior commissure.11-14 Lesions in any

of these structures can produce VSO, especially at the

thalamomesencephalic junction, which is regarded as im-

portant in the studies of VSO with unilateral lesions.13,14 GABAergic neurons in the pars reticulata of the substan-
tia nigra, which project to the tectum, are usually se-

creted in patients with idiopathic PSP.16 This is

also thought to contribute to eye movement abnormali-

ties, especially impairment in saccadic eye move-

ments.16 Yet, mesencephalic and nigral pathologic fea-

}

ures were absent in all patients. Recent clinical-
anatomical studies17,18 demonstrated that unilateral or

bilateral thalamic lesions can cause VSO. The location

of the lesions in the present series of patients with vas-

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Josephs, Ishizawa, Tsuboi, and Dickson); acquisition of
data (Drs Josephs and Dickson and Ms Cookson); analysis and interpretation of data (Dr Josephs); drafting of the manuscript (Dr Josephs); critical revision of the manuscript for important intellectual content (Drs Josephs, Ishizawa, Tsuboi, and Dickson and Ms Cookson); statistical expertise (Dr Dickson); obtained funding (Dr Dickson); administrative, technical, and material support (Drs Josephs, Ishizawa, Tsuboi, and Dickson and Ms Cookson); study supervision (Dr Dickson).

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REFERENCES