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 H2 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 H2 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 H2 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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STEELE 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 aggregates in specific cortical and subcortical locations, including the motor cortex, basal ganglia, thalamus, subthalamic nucleus, brainstem, and cerebellum. The clinical phenotype of the τ-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-
Patients With Vascular PSP.7,8,10

imaging, computed tomography, and an autopsy case of ganglia have been described using magnetic resonance cortex, striatum, corona radiata, internal capsule, and basal pons, substantia nigra, centrum semiovale, frontal sub-

sequently, Binswanger disease presenting as PSP was de-

asymmetric and lower body involvement. Subse-

lar PSP

asymptomatic and lower body involvement. Subsequently, Binswanger disease presenting as PSP was described.12-14 Infarcts in the unilateral thalamomesencephalic and rostral interstitial 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 thalamomesencephalic and rostral interstitial medial longitudinal fasciculus lesions.12-14 Infarcts in the pons, substantia nigra, centrum semiovale, frontal sub-

cortex, 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.7,8,10

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 de-

fined.7-9 To our knowledge, this is the largest clinico-

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>
</tr>
</thead>
<tbody>
<tr>
<td>Sex/age at death, y</td>
<td>M/87</td>
<td>M/72</td>
</tr>
<tr>
<td>Haplotype</td>
<td>H1/H1</td>
<td>H1/H2</td>
</tr>
<tr>
<td>Disease duration, y</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td>Falls 1 y after symptom onset</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Early dysarthria/dysphagia</td>
<td>+</td>
<td>–</td>
</tr>
<tr>
<td>Levodopa resistance</td>
<td>NA</td>
<td>+</td>
</tr>
<tr>
<td>Axial rigidity</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Asymmetric features</td>
<td>L Babinski sign</td>
<td>R rigidity and resting tremor</td>
</tr>
<tr>
<td>Other features</td>
<td>Retrocollis and hypomimia</td>
<td>Bradykinesia</td>
</tr>
<tr>
<td>HTN</td>
<td>NA</td>
<td>+</td>
</tr>
<tr>
<td>MRI/CT findings</td>
<td>Increased T2-weighted signal in the corona radiata and the centrum semiovale</td>
<td>Lacunar infarcts in the R basal ganglia and the caudate and lentiform nuclei</td>
</tr>
</tbody>
</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 PSP5 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 determination 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.15

RESULTS

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 were also reported. All 4 patients had asymmetric findings on examination, including cranial nerve VII palsy (n = 2), hemiparesis, the Babinski sign, tremor, rigidity, or leg dystonia. One patient had magnetic resonance imaging evidence of lacunar infarcts in the basal ganglia, 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 τ pathologic features in any patient. Similarly, the substantia nigra, superior colliculus, periaqueductal gray matter, and cerebellar deep nuclei were free of infarcts and τ pathologic features. A microscopic examination in all 4 patients showed small cerebellar infarcts that were not detected on gross inspection. τ Haplotypes in all 4 patients showed small cerebellar infarcts that were not detected on gross inspection. τ Haplotype analysis revealed an H2/τ haplotype in 3 of the 4 patients (2 had the H1/H2 τ genotype and 1 had the H2/H2 τ genotype).

### 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>Infarcts in Patients With Vascular PSP</th>
<th>NFTs in Patients With Pathologically Proved PSP</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1 R L 2 R L 3 R L 4 R L</td>
<td></td>
</tr>
<tr>
<td>Frontal lobe</td>
<td>+ + + + + + + + + + + + + + + + +</td>
<td></td>
</tr>
<tr>
<td>Temporal lobe</td>
<td>- - - - - - - - - - - - - - - - -</td>
<td></td>
</tr>
<tr>
<td>Parietal lobe</td>
<td>++ + + + + + + + + + + + + + + +</td>
<td></td>
</tr>
<tr>
<td>Caudate/putamen</td>
<td>- - + - - - - - - - - - - - - -</td>
<td></td>
</tr>
<tr>
<td>Globus pallidus</td>
<td>- - - - - - - - - - - - - - - - -</td>
<td></td>
</tr>
<tr>
<td>Basal nucleus</td>
<td>- - - - - - - - - - - - - - - - -</td>
<td></td>
</tr>
<tr>
<td>Thalamus</td>
<td>++ + + + + + + + + + + + + + + +</td>
<td></td>
</tr>
<tr>
<td>Subthalamic nucleus</td>
<td>- - - - - - - - - - - - - - - - -</td>
<td></td>
</tr>
<tr>
<td>Red nucleus</td>
<td>- - - - - - - - - - - - - - - - -</td>
<td></td>
</tr>
<tr>
<td>Substantia nigra</td>
<td>- - - - - - - - - - - - - - - - -</td>
<td></td>
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<tr>
<td>Oculomotor nerve complex</td>
<td>- - - - - - - - - - - - - - - - -</td>
<td></td>
</tr>
<tr>
<td>Superior colliculus/periaqueductal gray matter</td>
<td>- - - - - - - - - - - - - - - - -</td>
<td></td>
</tr>
<tr>
<td>Locus coeruleus</td>
<td>- - - - - - - - - - - - - - - - -</td>
<td></td>
</tr>
<tr>
<td>Pontine tegmentum</td>
<td>- - - - - - - - - - - - - - - - -</td>
<td></td>
</tr>
<tr>
<td>Pontine base</td>
<td>- + - - - - - - - - - - - - - - -</td>
<td></td>
</tr>
<tr>
<td>Medullary tegmentum</td>
<td>- - - - - - - - - - - - - - - - -</td>
<td></td>
</tr>
<tr>
<td>Inferior olive</td>
<td>- - - - - - - - - - - - - - - - -</td>
<td></td>
</tr>
<tr>
<td>Dentate nucleus</td>
<td>- - - - - - - - - - - - - - - - -</td>
<td></td>
</tr>
<tr>
<td>Cerebellar white matter</td>
<td>- - - - - - - - - - - - - - - - -</td>
<td></td>
</tr>
<tr>
<td>Cerebellar cortex</td>
<td>+ - - - + + + + - - - - - - - -</td>
<td></td>
</tr>
</tbody>
</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.
†Mild to moderate NFT density.
‡Moderate to severe NFT density.

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. Retrocollis 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-
of the lesions in the present series of patients with vas-
bilateral thalamic lesions can cause VSO. The location
of 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, because all patients had VSO, parkinsonism, and frequent falls. Furthermore, there was never any apparent episodic deteriora-
tion in their histories suggestive of isolated or multiple
episodes. 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 al for possible or prob-
able PSP because of the late onset of falls, asymmetric
signs, and neuroradiologic abnormalities. Winikates and
Jankovic suggested that vascular PSP should be differ-
niated from idiopathic PSP if the patient has a higher
degree of asymmetry, lower body involvement, evi-
dence of corticospinal and pseudobulbar signs, some neu-
roimaging 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-
ginning 1 year after symptomatic onset was a common
feature in all 4 patients and may be another differenti-
ating feature. Magnetic resonance imaging is also impor-
tant for detecting vascular lesions, because thalamic and
unilateral or bilateral striatal involvement, which may be
difficult to detect with computed tomographic scans,
seems crucial for the development of vascular PSP.

Baker et al demonstrated increased frequency of a
particular form of the extended \( \tau \) haplotype (the H1 \( \tau \)
 haplotype) in patients with PSP compared with normal
control subjects, with frequencies of 93.7% in those with
PSP compared with 78.4% in controls. In the present
series of patients with vascular PSP, 3 of the 4 patients car-
ried an H2\( \tau \) haplotype, including 1 who was homozy-
gous for H2, a rare occurrence in the general population.
These results raise the possibility that determination of
the \( \tau \) haplotype may be an ancillary aid in the differen-
tial diagnosis of vascular PSP, but a larger study is needed
to confirm this observation.

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Author contributions: Study concept and design (Drs
Josephs, Ishizawa, Tsuboi, and Dickson); acquisition of

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 slilike 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.
REFERENCES