



## Cerebrovascular pathology and misdiagnosis of multiple system atrophy: An autopsy study



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### ABSTRACT

**Background:** Multiple system atrophy (MSA) is a progressive neurodegenerative disease characterized by a combination of dysautonomia, parkinsonism, and cerebellar ataxia. Other disorders can mimic MSA, but it is unknown whether cerebrovascular pathology, so-called “vascular parkinsonism,” can mimic MSA. This study aimed to determine the clinicopathological features and red flags for vascular parkinsonism masquerading as MSA.

**Methods:** Using a brain bank database, we screened 270 patients with an antemortem diagnosis of MSA, who did not have pathologic evidence of MSA, but rather cerebrovascular pathology, including leukoencephalopathy, lacunar infarcts, and microinfarcts. Histologic sections from the neocortex, basal ganglia, thalamus, brainstem, and cerebellum were reviewed. Medical records were reviewed to characterize the clinical features. The probability of a clinical diagnosis of MSA was assigned retrospectively, guided by current consensus criteria.

**Results:** Four patients had cerebrovascular pathology without neurodegenerative processes. Chronic ischemic changes in periventricular white matter, subcortical leukoencephalopathy, lacunar infarcts, or microinfarcts were detected in basal ganglia of all patients. Cerebrovascular pathology that might contribute to autonomic failure was not identified. Clinically, two patients were diagnosed with possible MSA-parkinsonism, one with probable MSA-parkinsonism, and one with possible MSA-cerebellar type; however, they also had one or more non-supporting features of MSA (e.g., onset > 75-years of age, dementia), vascular risk factors, and other etiologies (e.g., autonomic neuropathy) that could cause autonomic failure.

**Conclusions:** When combined with cerebrovascular risk factors and comorbidities, cerebrovascular pathology may masquerade as MSA. The important lesson from this study is that the diagnosis of MSA requires exclusion of other causes, including cerebrovascular disease.

### 1. Introduction

Multiple system atrophy (MSA) is a progressive neurodegenerative disease characterized by a combination of autonomic failure, parkinsonism, and cerebellar ataxia [1]. The current consensus diagnostic criteria for MSA define three degrees of certainty: definite, probable, and possible [1]. A diagnosis of definite MSA requires pathologic confirmation. Neuronal loss and gliosis in striatonigral and olivopontocerebellar systems, as well as glial cytoplasmic inclusions composed of  $\alpha$ -synuclein, are the pathologic hallmarks of MSA [2]. A diagnosis of probable or possible MSA requires autonomic failure with parkinsonism and/or cerebellar involvement in which other causes are excluded [1].

Diagnostic specificity of the criteria is suboptimal [3]. Patients with other neurodegenerative or non-neurodegenerative diseases are sometimes diagnosed with MSA [4–6]. Autopsy-based studies on clinical diagnostic accuracy of MSA have shown that dementia with Lewy bodies, progressive supranuclear palsy, and Parkinson's disease are common causes of misdiagnosis [4,6]. In addition, about 1% of autopsy cases have cerebrovascular pathology without any other neurodegenerative pathology to account for the MSA-like syndrome [4,6].

Accumulating evidence indicates that cerebrovascular pathology, including multiple ischemic lesions in basal ganglia, thalamus, and subcortical white matter, can present with parkinsonism, which is referred to as “vascular parkinsonism” [7–9]. Vascular parkinsonism

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**Table 1**  
Clinical summary of four vascular MSA patients.

	Case 1	Case 2	Case 3	Case 4
Age at death	74	88	69	57
Sex	M	M	M	M
Disease duration, years	4	6	3	11
Clinical diagnosis	MSA-P	MSA-P	MSA-P	MSA-C
Autonomic failure	+	+	+	+
Orthostatic hypotension	-	+	+	+
Urinary incontinence	+	+	+	-
Sudomotor dysfunction	+	+	NA	+
Parkinsonism	+	+	+	-
Cerebellar ataxia	+	+	-	+
Pyramidal signs	-	-	-	-
Cognitive impairment	-	-	+	-
Hallucinations	-	+	-	-
REM sleep behavior disorder	-	-	-	-
Depression	-	+	+	-
Peripheral neuropathy	+	-	-	+
Hypertension	+	+	+	-
Dyslipidemia	+	-	-	+
Diabetes mellitus	+	-	+	-
Transient ischemic attack	-	-	-	-
Stroke	+	-	-	-
Autonomic reflex screen	+	+	Urodynamic test	+
Specialty of physicians	Autonomic disorders; Movement disorders	Autonomic disorders; Movement disorders	Movement disorders	General neurology
Supporting features	Anterocollis	Myoclonus	-	-
Non-supporting features	Neuropathy	Hallucinations; onset after 75 years old	Dementia	Neuropathy

+ indicates presence; - indicates absence of symptoms, signs or past medical history. NA indicates not available in medical records.

usually has an insidious onset and symmetric, lower body-predominant parkinsonism [10]. Some patients with vascular parkinsonism can mimic progressive supranuclear palsy or corticobasal syndrome [11–14]. Glass et al. reported clinical features of 28 patients with vascular parkinsonism, and two were clinically diagnosed with MSA [10]. Taken together, a few patients with vascular parkinsonism present as MSA, but their pathology has not been studied in detail.

We herein describe four patients with a clinical diagnosis of MSA in which cerebrovascular pathology was considered to be the likely cause of many of the clinical manifestations. All patients presented with autonomic dysfunction with parkinsonism or cerebellar ataxia; however, they also had one or more non-supporting features of MSA, as well as vascular risk factors. This case series emphasizes that exclusion of other etiologies is important before applying diagnostic criteria for MSA.

## 2. Materials and methods

### 2.1. Subjects

Cases included in this study were from the Mayo Clinic brain bank and acquired between 1998 and 2019. During this time frame, 270 patients had an antemortem diagnosis of MSA, of which 184 had autopsy-confirmed MSA, 82 had other neurodegenerative disorders, and four cases had primarily cerebrovascular disease. We systematically evaluated the clinical and pathologic features of those with cerebrovascular disease. Autopsies on all cases were performed with the consent of the legal next-of-kin or an individual with power-of-attorney. Studies on de-identified autopsy samples are considered exempt from human subject research by the Mayo Clinic Institutional Review Board.

### 2.2. Neuropathological assessment

All cases underwent a standardized neuropathological assessment of formalin-fixed left hemibrains, including macroscopic evaluation, hematoxylin-eosin stains, thioflavin S fluorescent microscopy, and immunohistochemistry for  $\alpha$ -synuclein (NACP, 1:3000, Mayo Clinic antibody, FL) [15], phospho-tau (CP13, 1:1000, from Dr. Peter Davies, Feinstein Institute, North Shore Hospital, NY), and phospho-TDP-43

(pS409/410, 1:5000, Cosmo Bio, Tokyo, Japan). Brain regions sampled included neocortex (x6), hippocampus (x2), amygdala, basal ganglia (x2), thalamus, midbrain, pons, medulla, and cerebellum (x2). Cerebrovascular pathologies that were assessed included macroscopic and microscopic infarcts and hemorrhages, foci of ischemic gliosis, dilation of perivascular spaces (cribriform change), and leukoencephalopathy. Assessment of large and small vessels in the brain parenchyma, leptomeninges, and at the base of the brain (Circle of Willis) was assessed for the presence and severity of arteriolosclerosis, atherosclerosis, and cerebral amyloid angiopathy. Luxol fast blue staining was used to confirm white matter pathology in cases with leukoencephalopathy. Braak neurofibrillary tangle (NFT) stages and Thal amyloid phases were assigned based upon the distribution of amyloid plaques and NFT with thioflavin S fluorescent microscopy [16–18].

### 2.3. Clinical assessment

The following clinical information was abstracted from available medical records by three investigators (SK, SFR, PWT): demographic information, clinical diagnoses, past medical history, risk factors for cerebrovascular disease, imaging findings, autonomic function testing, clinical symptoms, and neurological signs. We focused on autonomic failure (e.g., orthostatic hypotension, urinary problems, and erectile dysfunction), parkinsonism (e.g., resting tremor, cogwheel rigidity, postural instability, and bradykinesia), and cerebellar ataxia [1]. The specialty of physicians who evaluated patients (i.e., movement disorder specialist, autonomic disorder specialist) was also noted.

## 3. Results

### 3.1. Demographic and clinical features of MSA

We identified four patients with a clinical diagnosis of MSA who lacked MSA pathology but instead had cerebrovascular pathology. Demographic and clinical features of vascular MSA are summarized in Table 1.

Case 1 was a 74-year-old Caucasian man with a history of hypertension, dyslipidemia, and long-standing insulin-dependent diabetes

mellitus with subsequent retinopathy, peripheral neuropathy, and chronic kidney disease. He was initially evaluated by a movement disorders specialist at age 71, at which time he described a one-year history of progressive changes in his posture with shuffling gait and falls. He was diagnosed with Parkinson's disease and started on levodopa, which resulted in improved facial expression and less shuffling when walking. Neurological examination was notable for hypomimia, slowed saccadic eye movements, mixed dysarthria with ataxic and hyperkinetic features, diffuse areflexia, anterocollis, rigidity most pronounced in the neck, postural instability, and gait abnormalities, including decreased arm swing, impaired tandem walking, and turning en bloc. He required 10 steps to turn 360°. Vasomotor, sudomotor, and trophic changes were noted in the distal extremities.

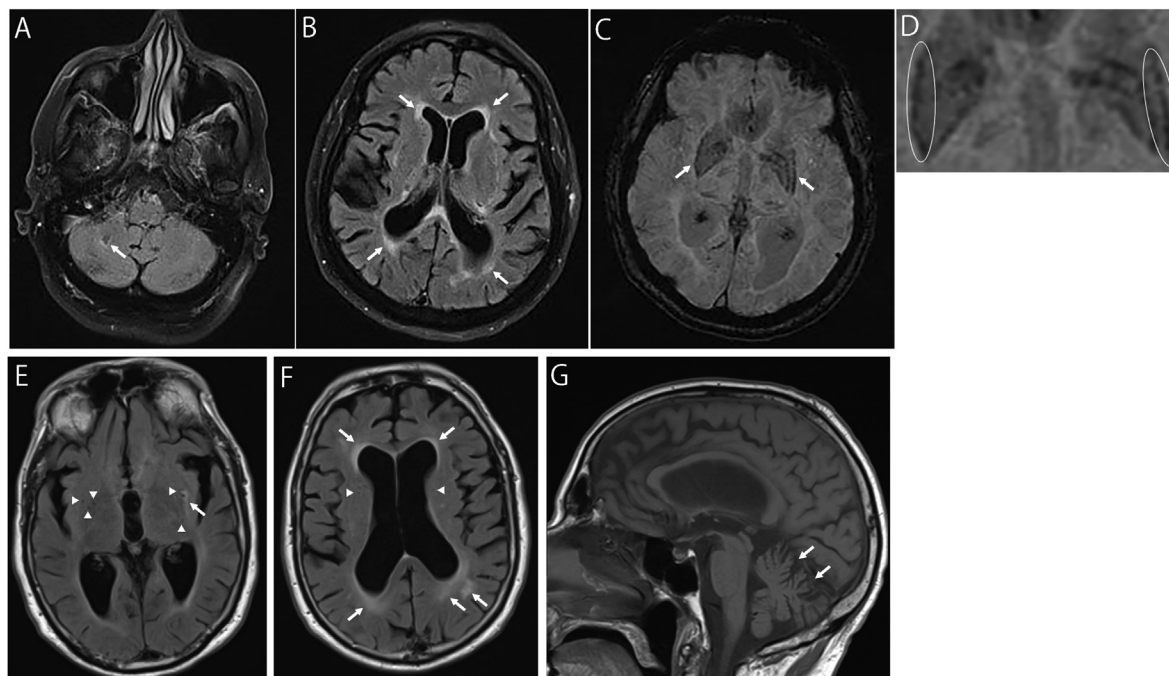
Autonomic reflex screen showed generalized autonomic failure as evidence by a composite autonomic severity score (CASS) of 7 (CASS: 0 = none, 1-3 = mild, 4-6 = moderate and 7-10 = severe [19]) with cardiovagal, sudomotor, and adrenergic impairment. Orthostatic hypotension was not present. He developed urinary incontinence, but urinary retention was not noted. MRI of the brain demonstrated a chronic lacunar infarct in the right cerebellar hemisphere, as well as bilateral subcortical lacunar infarcts, and both subcortical and periventricular FLAIR sequence hyperintensities consistent with small vessel ischemic changes. Axial susceptibility-weighted imaging showed hypointensities in the lateral putamen, which was suggestive of MSA (Fig. 1A–D) [20]. Based on parkinsonism, autonomic failure, anterocollis, and MRI findings, he was clinically diagnosed with possible MSA-P [1].

Case 2 was an 88-year-old Caucasian man with a history of hypertension and depression. At the age of 82, he had an affective disorder with paranoid ideation, delusional thinking, and non-threatening auditory hallucinations. Symptoms improved with haloperidol; however, the development of parkinsonism prompted a medication change to aripiprazole and venlafaxine. He developed gait impairment leading to falls, and he poorly responded to dopaminergic medications. He developed urinary incontinence and orthostatic hypotension, which

was treated with midodrine and fludrocortisone. At age 85, his examination revealed symmetrical bradykinesia, mild-to-moderate cogwheel rigidity, short stride length with ataxic features, and postural instability. Autonomic reflex screen showed mild-to-moderate cardiovascular adrenergic impairment and patchy postganglionic sympathetic sudomotor abnormalities. CASS was 4. Brain MRI revealed mild dilation of the lateral ventricles, cerebellar atrophy, and moderate chronic ischemic changes within the deep white matter, subcortical white matter, and lateral basal ganglia bilaterally (Fig. 1E–G). Based on levodopa unresponsive parkinsonism, the lack of resting tremor, and severe autonomic failure, he was clinically diagnosed with possible MSA-P.

Case 3 was a 69-year-old Caucasian man who had multiple vascular risk factors, including hypertension, diabetes, obesity, and coronary artery disease, as well as a surgical history of coronary artery bypass graft, pacemaker implantation, and resection of metastatic melanoma. He had erectile dysfunction since age 63. At age 66, he presented with urinary incontinence, syncope, difficulty with gait and balance, anxiety disorder with mood swings and cognitive impairment characterized by disorientation, forgetfulness, and bradyphrenia. He had orthostatic hypotension, and he was prescribed fludrocortisone. At age 67, his neurological examination revealed bradykinesia, symmetric upper extremity rigidity, intention tremor, incoordination of the left arm, micrographia, postural instability, wide-based shuffling gait, and prominent square wave jerks. He developed dysphagia with a softened voice. Urodynamic testing revealed neurogenic bladder dysfunction. A CT scan of the head showed changes consistent with small vessel ischemic pathology in periventricular white matter. At age 68, he scored 18/30 on the Mini-Mental Status Examination. He was treated with levodopa, but the responsiveness was not documented. Based on the combination of autonomic failure and parkinsonism, he was clinically diagnosed with probable MSA-P.

Case 4 was a 57-year-old Caucasian man who had a history of dyslipidemia and peripheral neuropathy. At the age of 46, he underwent evaluation for a wide-based gait. Autonomic reflex screen showed mild distal postganglionic sudomotor impairment and normal



**Fig. 1.** Brain MRI findings of a patient (Case 1) at age 71 (A–D) and a patient (Case 2) at age 85 (E–G). Axial FLAIR sequences show a chronic lacunar infarct (arrow) in the right cerebellar hemisphere (A) and extensive small vessel disease with subcortical lacunar infarcts (B, arrows). Axial susceptibility-weighted imaging sequences show hypointensities (arrows) in the lateral putamen (C, D). Axial FLAIR sequences reveal dilation of vessels (arrowheads) in the putamen, hyperintensities (arrows) in the left lateral putamen (E), hyperintensities (arrows) in the periventricular, and subcortical white matter (F). A sagittal section on T1-weighted image discloses cerebellar atrophy (G, arrows). Lateral ventricles are moderately enlarged in the both patients (B, E–G).

**Table 2**  
Pathological features and Infarct distribution in patients with vascular MSA.

Pathologic features	Case 1	Case 2	Case 3	Case 4
Brain weight, g	1080	1240	1120	1320
Braak neurofibrillary tangle stage	II	III	II	0
Thal amyloid phase	2	3	1	0
Arteriosclerosis/atherosclerosis	+/+	+/+	+/+	-/-
Cerebral amyloid angiopathy	-	-	-	-
<b>Infarct distribution</b>				
Frontal lobe	-	-	-	-
Temporal lobe	-	-	-	-
Parietal lobe	-	-	++ <sup>a</sup>	-
Occipital lobe	-	-	-	+ <sup>a</sup>
Motor cortex	-	-	-	-
Periventricular white matter	+	+	+	+
Subcortical leukoencephalopathy	+	+	+	+
Caudate/putamen	+	+	++	++
Globus pallidus	+	-	-	++
Basal nucleus	+	-	-	-
Thalamus	+	+	-	++
Hypothalamus	-	-	-	+
Subthalamic nucleus	-	-	-	+
Amygdala	+	-	-	-
Hippocampus	+	-	-	-
Red nucleus	-	-	-	-
Substantia nigra	-	-	+	-
Oculomotor nerve complex	-	-	-	-
Superior colliculus	-	-	-	-
Locus coeruleus	-	-	-	-
Pontine tegmentum	-	-	-	-
Pontine base	-	+	+	-
Medullary tegmentum	-	-	-	-
Inferior olivary nucleus	-	-	-	-
Cerebellum	-	-	-	-

<sup>a</sup> Acute hemorrhagic infarct. + indicates microinfarct and ++ indicates macroscopic infarct.

adrenergic and cardiovagal function with normal orthostatic blood pressure. His CASS was 1. He subsequently developed autonomic failure, including orthostatic hypotension, frequent urination, and xerostomia. At age 56, his neurological evaluation was notable for intention tremor and upper extremity incoordination, suggestive of cerebellar ataxia. He was diagnosed with possible MSA-C.

### 3.2. Pathological features of vascular MSA

Pathological features of vascular MSA are summarized in Table 2. By definition, none of the patients had  $\alpha$ -synuclein pathology consistent with MSA, nor did they have Lewy-related pathology, tauopathy, or TDP-43 proteinopathy. Instead, all four patients had arteriosclerotic vascular pathology with chronic ischemic changes in periventricular white matter, as well as more extensive subcortical leukoencephalopathy. Microscopic infarcts were detected in all four patients; the putamen was most often affected, followed by the thalamus. Alzheimer-type pathology was minimal; the mean Braak NFT stage was II, and the mean Thal amyloid phase was 1.

Case 1 had no apparent cerebrovascular pathology in the left hemisphere on gross examination. Microscopically, the neocortex was relatively unremarkable. The subcortical and deep white matter had diffuse myelinated fiber loss and gliosis, in addition to the multiple small cystic or partially cystic chronic infarcts (Fig. 2A and B). The periventricular white matter had extensive ischemic softening and gliosis (Fig. 2C and D). The blood vessels in the cerebral white matter had severe arteriosclerotic hyalinosis, and there were collagen deposition and blood pigment in the perivascular spaces (Fig. 2E). There were small chronic infarcts in the hippocampus (Fig. 2F) and basolateral amygdala (Fig. 2G). The basal ganglia were remarkable for severe arteriosclerotic small vessel disease, with cribriform change and multiple microinfarcts and a larger lacunar infarct in the putamen. There was

also a slit-like lesion filled with hemosiderin-filled macrophages, consistent with a small chronic hemorrhage (Fig. 2H). There was marked cribriform change in the globus pallidus. The thalamus had arteriosclerotic small vessel disease, with cribriform change and multiple microinfarcts, as well as a cystic lacunar infarct. There was focal Wallerian degeneration in the internal capsule.

Case 2 had no apparent cerebrovascular pathology in the left hemisphere on gross examination. Microscopic examination revealed an infarct in the periventricular white matter, associated with diffuse atrophy, dilation of perivascular spaces, and gliosis throughout the centrum semiovale (Fig. 2I and J). Severe arteriosclerosis was observed in the lenticulostriate arteries (Fig. 2K). The pontine base also had an infarct (Fig. 2L).

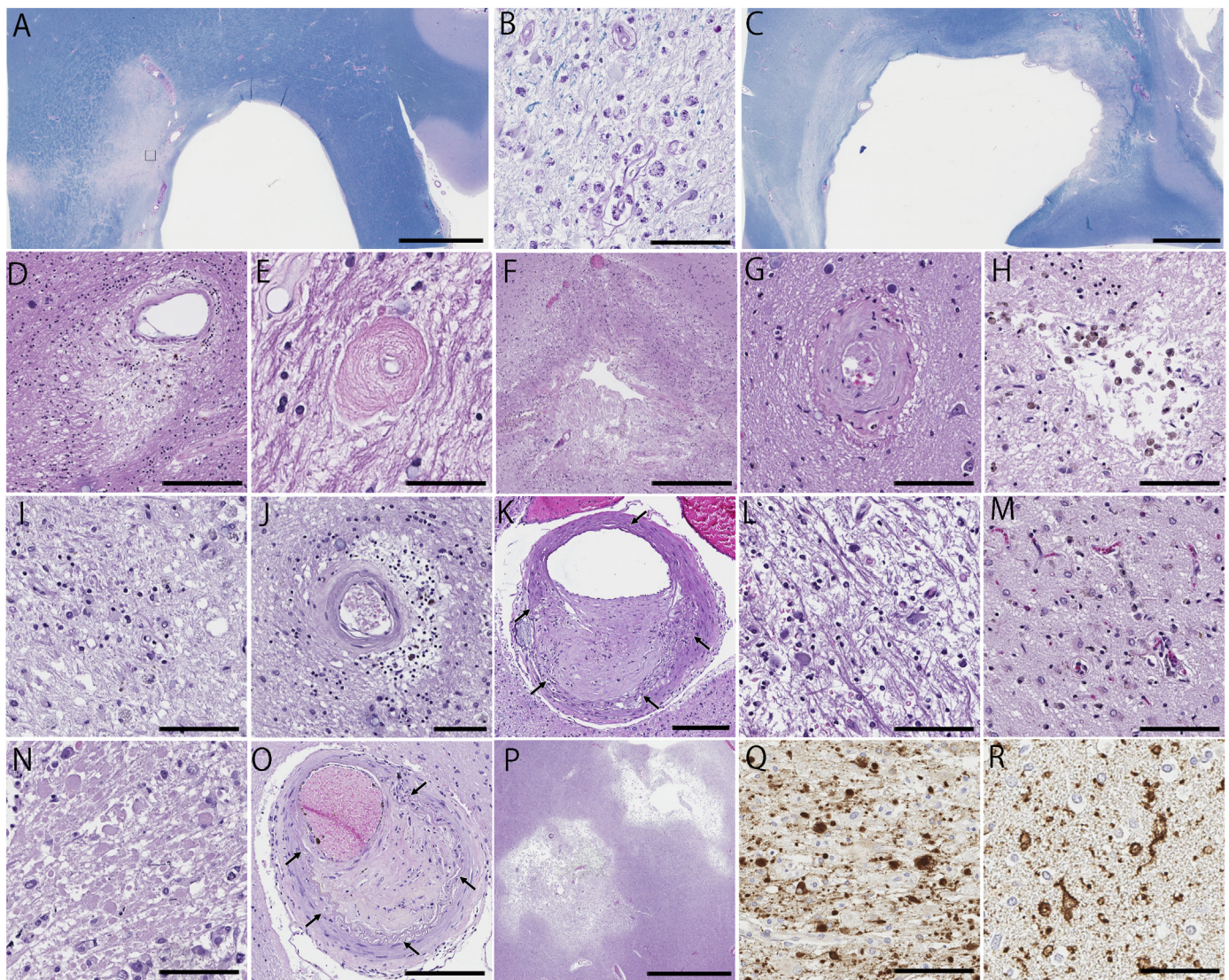
Case 3 had no apparent cerebrovascular pathology in the left hemisphere on gross examination. Microscopic examination revealed several small infarcts in the caudate nucleus (Fig. 2M) and pontine base (Fig. 2N), as well as microinfarcts in the lateral geniculate nucleus and foci of ischemic gliosis in the globus pallidus. There was also subcortical arteriosclerotic leukoencephalopathy. Dilation of perivascular spaces, arteriosclerosis, and atherosclerosis were observed in the cortex and basal ganglia (Fig. 2O).

Case 4 had an acute hemorrhagic infarct in cortical gray and subcortical white matter in the left occipital lobe on gross examination. The basal ganglia had partially cystic infarcts affecting most of the globus pallidus, as well as the medial and rostral parts of the putamen (Fig. 2P). The infarcts were filled with lipid-laden macrophages, and there was gliosis with numerous spheroids in the surrounding tissues (Fig. 2Q). The thalamus, hypothalamus, subthalamic nucleus, and posterior limb of internal capsule had large partially cystic infarcts, similar in histologic age to the lesions in the basal ganglia. White matter tracts caudal to the infarcts had vacuolation with activated macrophages, consistent with early Wallerian degeneration (Fig. 2R).

## 4. Discussion

In this retrospective clinicopathological study based on a referral brain bank, we identified four patients with clinically diagnosed MSA who failed to meet pathologic criteria for MSA. Instead, each patient had cerebrovascular pathology as the best explanation for their clinical presentations. Several autopsy studies have suggested that vascular parkinsonism can mimic MSA; however, cerebrovascular pathology was not described [4,6,10]. To our knowledge, this is the largest clinicopathological study of vascular MSA.

Antemortem clinical diagnosis of MSA is reasonable in these cases; however, had “red flags” against MSA been considered, it may have increased diagnostic accuracy. The criteria explicitly state this caveat for autonomic failure: other disorders known to cause orthostatic hypotension, such as diabetes mellitus with autonomic neuropathy, should be excluded or at least taken into account [1]. On the other hand, the criteria do not explicitly mention similar consideration of vascular and drug-induced mechanisms as possible causes of parkinsonism [1,3]. Case 1 had the diabetic triad of neuropathy, retinopathy, and nephropathy, as well as generalized autonomic failure. Autonomic abnormalities in this patient are better ascribed to diabetic autonomic neuropathy. This finding, as well as MRI evidence of cerebrovascular pathology, should have led to a diagnosis of vascular parkinsonism with diabetic autonomic neuropathy. Case 2 had multiple “red flags” against MSA. The patient was 85 at the age of onset, had affective symptoms and persistent hallucinations, which suggest a diagnosis other than MSA. Moreover, the development of parkinsonism was noted only after haloperidol. He had a relatively low CASS score, and he had MRI changes more suggestive of vascular disease than MSA. Case 3 had a clinical phenotype dominated by cognitive and affective complaints, as well as multiple vascular risk factors and CT findings supportive of vascular disease. Case 4 had neuropathy. The major lesson from a review of these four cases is that a diagnosis MSA requires exclusion of



**Fig. 2.** Representative microscopic findings of cerebrovascular pathologies from four patients. Case 1 has a chronic infarct with myelinated fiber loss in the periventricular white matter (A). A higher magnification of the pale staining area in A shows PAS-positive macrophages and myelin loss (B). Extensive myelin staining pallor (C) and tissue rarefaction with hemosiderin pigment (D) are seen in the periventricular white matter. A blood vessel in the deep white matter shows severe narrowing of the lumen due to hyalinosis (E). A cystic infarct is present in the hippocampus (F), and severe arteriosclerosis is noted in the amygdala (G). Case 2 has a microscopic partially cystic infarct with hemosiderin pigment in the periventricular white matter (H) and chronic ischemic foci with macrophages (I). A small vessel shows arteriosclerosis with perivascular hemosiderin (J). Severe atherosclerosis with a fibrohyaline intimal plaque (arrows show boundary of the internal elastic lamina) is observed in lenticulostriate arteries (K), and a microscopic infarct is noted in the pons (L). Case 3 has microscopic infarcts in the caudate (M) and pons (N), as well as severe atherosclerosis in lenticulostriate arteries (O). Case 4 has multiple chronic cystic infarcts in the putamen and globus pallidus (P). The internal capsule near the infarct in the putamen has numerous axonal spheroids (Q). The fiber tracts caudal to the infarct have vacuolation with macrophages, consistent with Wallerian degeneration (R). A–C: Luxol fast blue stain; D–P: hematoxylin-eosin stain.; Q: immunohistochemistry for amyloid precursor protein (APP); R: immunohistochemistry for IBA-1. Bars: 4 mm in A, C, and P; 500  $\mu$ m in F; 200  $\mu$ m in D, K, and O; 100  $\mu$ m in B, G–J, L–N, Q, and R; 50  $\mu$ m in E. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

alternative etiologies for both autonomic and extrapyramidal signs before applying the consensus criteria. We suggest that the presence of multiple vascular risk factors supported by cerebrovascular pathology in the subcortical gray matter on neuroimaging studies should be considered evidence for possible vascular parkinsonism and “red flags” against a diagnosis of MSA.

Autonomic dysfunction in vascular parkinsonism is a challenge [10,21]. A previous study of pathologically confirmed vascular parkinsonism found urinary incontinence and constipation in about half the patients, while 25% had orthostatic hypotension [10]. Several studies demonstrate that lesions in brainstem autonomic centers, including ventrolateral medulla and solitary nucleus, periaqueductal gray matter in the midbrain, hypothalamus, amygdala, and insular cortex

may all play a role in autonomic dysfunction [22–25]. In the present study, however, the medulla, midbrain, hypothalamus, and amygdala were not consistently affected. Bladder dysfunction is a common non-motor symptom of Parkinson's disease and thought to be related to altered dopamine-basal ganglia circuitry, which normally suppresses the micturition reflex [26]. The basal ganglia are usually affected in vascular parkinsonism, and there was gross or microscopic evidence of basal ganglia pathology in all four patients.

The correlation between cerebrovascular pathology and clinical presentation of MSA should be interpreted cautiously. Given the fact that all patients had infarcts in subcortical and perivascular white matter, white matter damage may be associated with the clinical presentation of MSA. All patients had striatal lesions, which can be

associated with parkinsonism. In contrast, Case 4 was considered to have cerebellar ataxia, but no apparent lesions were found in the cerebellum and related structures on the side of the brain evaluated. Given that the patient had significant neuropathy, sensory ataxia may have been misinterpreted as cerebellar ataxia [27]. The brain MRI of case 2 revealed *ex vacuo* ventricular enlargement, but there were no other radiographic findings to suggest normal pressure hydrocephalus (e.g., disproportionately enlarged subarachnoid space hydrocephalus). Gait abnormalities may have been related to the disruption of frontal sub-cortical systems by ischemic white matter pathology [28].

There are some limitations in our study. Given the retrospective nature of the study, the referral basis of the brain bank, limited clinical information in some cases (particularly Case 4 where medical records were not available between ages 46 and 56), it was not always possible to rigorously confirm MSA clinical criteria. In addition, the diagnosis of MSA in Case 4 was not made by a movement disorder or autonomic disorder specialist. Another limitation is that only hemibrains were evaluated neuropathologically. Had the other side been evaluated additional cerebrovascular pathology might have been found. Assessment of peripheral nervous system and spinal cord was not possible, but would have been helpful to rule out sensory ataxia due to peripheral neuropathy and non-cerebellar causes of ataxia.

The strength of our study was post-mortem characterization of brain pathology linked with documentation of antemortem clinical syndromes. Previous studies have discussed clinicopathological correlates of vascular parkinsonism based on antemortem imaging studies; however, ischemic changes such as “white matter disease” or “leukoaraiosis” do not necessarily reflect cerebrovascular pathology at autopsy [29]. Histopathologic analysis is needed to clarify the correlation between vascular pathology and parkinsonism.

In summary, we identified four patients with cerebrovascular pathology as the likely pathologic substrate of antemortem clinical diagnoses of MSA. We did not, however, find convincing cerebrovascular pathology that might contribute to autonomic dysfunction, particularly orthostatic hypotension. Peripheral neuropathy, diabetes mellitus, and other etiologies might have been responsible for autonomic dysfunction [3,30]. Cerebrovascular pathology itself, or a combination of cerebrovascular pathology and additional processes, such as peripheral neuropathy, might have led physicians to misdiagnose MSA. For this reason, the use of the term “vascular MSA” is imprecise in describing patients with this combination of clinical and pathologic findings. Our study demonstrates that even though uncommon, it is important to rule out cerebrovascular disease in patients with clinical features of MSA, especially if patients have multiple vascular risk factors and neuroimaging findings consistent with vascular parkinsonism.

#### Author contributions

Shunsuke Koga: Conception and execution of the project; analysis and interpretation of data; Writing of the first draft Shanu F. Roemer: Review and critique; analysis and interpretation of data; Philip W. Tipton: Clinical data acquisition and review; composition, review, and critique of manuscript. Phillip A. Low: Review and critique; analysis and interpretation of data; Keith A. Josephs: Review and critique; analysis and interpretation of data; Dennis W Dickson: Conception and organization of the project; interpretation of data; review and critique.

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Dr. Roemer reports no disclosures.

Dr. Tipton reports no disclosures.

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