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Cerebrovascular pathology presenting as corticobasal syndrome: An autopsy case series of "vascular CBS"

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ABSTRACT

Background: The corticobasal syndrome (CBS) is heterogeneous in terms of postmortem neuropathology. While it has been previously studied with antemortem neuroimaging, clinicopathologic features of corticobasal syndrome associated with cerebrovascular pathology (vascular CBS) have yet to be reported.
Methods: To identify vascular CBS, we searched the database of the CurePSP Brain Bank for patients with a clinical diagnosis of CBS who failed to meet neuropathologic criteria for corticobasal degeneration (CBD) or other neurodegenerative disease processes, but who had significant cerebrovascular pathology. Hemibrains were assessed macroscopically and processed for histological assessment. Medical records were reviewed to characterize clinical features of vascular CBS.
Results: Of 217 patients with an antemortem diagnosis of CBS, we identified three patients with vascular CBS. Multiple infarcts in the watershed regions (frontal lobe and motor cortex), periventricular white matter, thalamus, and basal ganglia were observed in two patients. One patient had no cortical infarcts, but had multiple white matter infarcts and corticospinal tract degeneration. All were clinically thought to have CBS based on progressive asymmetric motor symptoms, including rigidity and apraxia, as well as cognitive impairment. Antemortem imaging studies showed findings of chronic cerebrovascular disease, with infarcts or white matter pathology.
Conclusions: This autopsy study of vascular CBS shows that, while rare, cerebrovascular pathology involving the frontal lobe, white matter tracts, basal ganglia, thalamus, and corticospinal tract can underlie clinical features suggestive of CBS. When neuroimaging suggests an alternative explanation, including chronic infarcts in critical regions, caution is merited in considering CBD as the underlying pathology.

1. Introduction

Corticobasal syndrome (CBS) is characterized by progressive asymmetric rigidity, apraxia, alien limb phenomena, myoclonus, cortical sensory loss, dystonia, and cognitive dysfunction [1,2]. The neuropathological substrate of CBS was once thought to be corticobasal degeneration (CBD), but it is increasingly recognized that progressive supranuclear palsy (PSP), Alzheimer's disease (AD), Lewy body disease (LBD), and other neurodegenerative diseases can also present with CBS [3,4]. In addition to neurodegenerative disorders, cerebrovascular pathology can also produce extrapyramidal signs or movement disorders [5–9]. Compared to idiopathic Parkinson's disease, vascular parkinsonism is characterized by bilateral and symmetric lower limb-predominant parkinsonism and absence of resting tremor [5,8]. In rare cases, vascular parkinsonism has presentations similar to PSP or multiple system atrophy (MSA) [10,11]. Patients with "vascular CBS" have been reported based on MRI findings, but none of the cases were confirmed at autopsy [12–15]; therefore, it remains uncertain whether they were devoid of neurodegenerative changes of corticobasal degeneration (i.e., mixed CBD and vascular pathologies).

We herein describe three patients who clinically fulfilled diagnostic criteria for CBS. All presented with insidious onset of asymmetric spasticity, apraxia, and bradykinesia. Previous strokes preceded the diagnosis by several years and were clinically considered unrelated to CBS. Neuropathologic analysis revealed cerebrovascular pathologies without any other neurodegenerative processes, consistent with vascular CBS.

2. Materials and methods

2.1. Subjects

All patients included in this study were from the Cure PSP Brain

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Table 1
Clinical summary of vascular CBS patients.

	CBS-1	CBS-2	CBS-3
Age at death	69	82	69
Sex	M	F	M
Disease duration, years	12	3	8
Clinical diagnosis	CBS	CBS	CBS
Evaluated physicians	2 Movement disorder specialists & 4 neurologists	1 Movement disorder specialist & 3 neurologists	1 Neurologist
Asymmetrical symptoms	L > R	L > R	R > L
Alien limb phenomena	+	–	NA
Limb dystonia	+	–	NA
Limb myoclonus	+	+	NA
Limb apraxia	+	+	+
Cortical sensory loss	–	–	–
Hyperreflexia	+	–	+
Paresis/spasticity	+	–	+
Urinary incontinence	+	–	NA
Pseudobulbar palsy	NA	+	NA
Cognitive impairment	+	+	+
Word finding difficulty	+	+	+
Medical history			
Ischemic heart disease	–	+	+ (stents)
Atrial fibrillation	–	+	–
Pacemaker/ICD	–	+	–
Hypertension	–	+	+
Dyslipidemia	+	+	+
Diabetes mellitus	+	+	–
Homocystinuria	+	–	–
Carotid artery stenosis	–	–	90%
Peripheral vascular disease	–	+	+
Transient ischemic attack	+	+	–
Stroke	+	+	+
Anticoagulant therapy	–	–	Aspirin 81 mg/day

Abbreviations: CBS, corticobasal syndrome; ICD, implantable cardioverter defibrillator; L, left; NA, not available for review; R, right.

Bank at Mayo Clinic in Jacksonville, Florida, collected between 1998 and 2018. During this time frame, 217 patients had an antemortem diagnosis of CBS. Patients having multiple differential diagnoses (e.g., CBS vs. PSP) were excluded. To identify vascular CBS, we searched the database for patients without other major neurodegenerative disease processes (e.g., AD, LBD, PSP, CBD, MSA, TDP-43 proteinopathy), but with cerebrovascular disease. All brain autopsies were performed with the consent of the legal next-of-kin or an individual with legal authority to grant permission. De-identified studies using these autopsy samples are considered exempt from human subject research by the Mayo Clinic Institutional Review Board.

2.2. Neuropathological assessment

Formalin-fixed hemibrains underwent systematic and standardized sampling with neuropathologic evaluation by a neuropathologist (DWD). The regions sampled for histopathology were the middle frontal gyrus, superior temporal gyrus, inferior parietal gyrus, pre-and post-central gyri, visual cortex, cingulate gyrus, anterior and posterior hippocampus, amygdala, basal nucleus of Meynert, lentiform nucleus, hypothalamus, thalamus at the level of the subthalamic nucleus, midbrain, pons, medulla, cerebellum, and cervical spinal cord. Paraffin-embedded 5-μm thick sections mounted on glass slides were stained with hematoxylin and eosin (H&E) or thioflavin S stains. Alzheimer-type pathology, including Braak neurofibrillary tangle stage and Thal amyloid phase, were assessed as previously described [16–18]. Tau, Lewy-related, and TDP-43 pathology were assessed using immunohistochemistry for phospho-tau (CP13, 1:1000, from Dr. Peter Davies, Feinstein Institute, North Shore Hospital, NY), α-synuclein (NACP, 1:3000, Mayo Clinic antibody) [19] and phospho-TDP-43 (pS409/410, 1:5000, Cosmo Bio, Tokyo, Japan), respectively. Vascular pathologies, including infarcts, hemorrhages, ischemic gliosis, cribriform change, arteriosclerosis, atherosclerosis, and cerebral amyloid angiopathy were assessed on H&E stained and thioflavin S stained sections. Select sections were processed with Luxol fast blue or Masson's trichrome stain and with immunohistochemistry for CD68 (1:1000, KP-1, DAKO, Carpinteria, CA) and GFAP (1:5000, GA-5, BioGenex, Fremont, CA).

For one case (CBS-2), 1-cm thickness coronal sections of frozen right hemibrain were assessed macroscopically for infarcts and hemorrhages because this patient had left-side predominant clinical symptoms, but the formalin-fixed hemibrain was left side (i.e., presumably less affected side).

2.3. Clinical assessment

The following clinical information was derived from the medical records, radiological reports, and brain bank questionnaires filled out by a close family member as described previously [20]. This included sex, age of onset, age at death, medical history, medication, imaging findings, clinical symptoms, neurological signs, and final clinical diagnosis. Particular focus was on CBS features, including asymmetrical rigidity and apraxia, myoclonus, cortical sensory loss, alien limb phenomena, pyramidal signs, and cognitive impairment. Given the retrospective nature of the study, the quality of medical records was variable, and only information confirmed by two neurologists was included (SK, SFR). To assess possible bias that might be related to clinical diagnosis, subspecialty and the number of physicians who evaluated patients (i.e., movement disorder specialist or general neurologist) were also noted.

3. Results

3.1. Clinical vignettes

Demographic and clinical features of vascular CBS patients are summarized in Table 1.

3.1.1. CBS-1

This patient was a 69-year-old Caucasian man who had a medical history of homocystinuria, dyslipidemia, diabetes mellitus, and migraine.

He did not receive any anticoagulant therapy, but was treated with vitamin B supplementations due to homocystinuria. At age 57, he complained of left foot drag, which his relatives had noticed for several months before the patient noticed. He also had trouble dropping things from his left hand. The symptoms steadily progressed, and he had numerous episodes of near falls. He also noticed trouble moving his left hand. His left side became increasingly stiff, and gradually he lost the ability to use his hand for any purposeful tasks. He complained of arm and leg cramps, especially at night. He had also developed urinary urgency and later, urinary incontinence. On initial examination at age 60, he had occasional word-finding difficulties, significant saccadic breakdown of smooth pursuit in both horizontal and vertical planes, left-sided spastic catch, left-sided hyperreflexia, and extensive plantar response. No bradykinesia or tremor was noted. Gait was spastic, with left hemiplegia and foot-drop. His symptoms continued to progress over the next two years. He complained that when yawning, his arm would elevate and move spontaneously, even though he had difficulties lifting the arm volitionally. He frequently lost track of where his left arm or leg was located. On examination, a spastic-dystonic left hemiparesis and hyperreflexia with clonus were noted. There was substantial left-sided apraxia. Cerebellar testing was unremarkable, but the evaluation was limited on the left due to severe apraxia and dystonic weakness. His gait was notable for increased dynamic tone and dystonic posture on the left extremities. A brain MRI showed asymmetric right hemisphere atrophy particularly in the frontal and temporal lobes, extending into parietal and occipital lobes, with right lateral ventricle dilation. T2-weighted images showed hyperintensities of the periventricular region suggestive of gliosis, low signal changes in the right basal ganglia, right cerebral peduncle, and right aspect of the pons. A clinical diagnosis of CBS was made based on the combination of progressive spasticity, dystonia, and apraxia.

3.1.2. CBS-2

This patient was an 82-year-old right-handed Caucasian woman with a medical history of atrial fibrillation, hypertension, hyperlipidemia, diabetes mellitus, aortic atherosclerosis, congestive heart failure, coronary artery disease, peripheral vascular disease, chronic kidney failure, and obstructive sleep apnea. She had a pacemaker. She underwent coronary artery bypass graft surgery and open-heart surgery with aortic valve replacement when she was 76 years of age. After surgery, she developed continuous slurred speech, poor balance, and neck stiffness. She was initially put on warfarin, but this was discontinued due to gastrointestinal bleeding. She had progressive worsening of gait and balance. She also had intermittent uncontrolled facial movements. A year later, she was evaluated for a transient episode of worsened slurred speech and left upper extremity weakness. A CT scan showed an old infarct in the left basal ganglia, but no acute lesions. Her gait deteriorated, and she had falling episodes. At age 81, she was referred to a movement disorder specialist due to facial tics affecting eye, neck, jaw, and mouth. A diagnosis of CBS seemed probable due to her cognitive impairment, marked asymmetric ideomotor apraxia in both upper extremities (L > R), rigidity (L > R), bradykinesia, myoclonus, and possible eyelid apraxia or blepharospasm. Additionally, she had neck rigidity, horizontal and upgaze nystagmus, pseudobulbar affect, as well as lower body negative myoclonus. A clinical trial included levetiracetam for myoclonus and baclofen for stiffness. A CT scan showed scattered deep white matter hyperintensities consistent with small vessel disease, chronic lacunar infarcts, and mild cerebral atrophy. Neuropsychological evaluation showed rapidly progressive cognitive decline and significant decreases in her Mini-Mental State Examination scores from 29/30 to 16/30 in less than two years. She also had deficits in expressive language skills, visuospatial construction, recall of verbal information, and frontal/executive functions. These findings were considered supportive of a neurodegenerative process, such as CBD.

3.1.3. CBS-3

This patient was a 69-year-old right-handed Caucasian man who had a medical history of hypertension, hyperlipidemia, stroke at age 51, severe peripheral and ischemic heart disease with two cardiac stents, peripheral cyanosis, claudication, and colorectal cancer. His medications included aspirin 81 mg daily as an anticoagulant therapy. He developed progressive right-sided weakness and stiffness, with occasional tremors at age 61. He also had slurring of speech, word-finding difficulties, and short-term memory problems. He had progressive difficulty using utensils and required a wheelchair. He was treated with carbidopa-levodopa at age 67, without response. At age 69, his neurological examination was notable for asymmetric rigidity (R > L), lower muscle weakness (R > L), and a Babinski sign on the right. He could follow simple, but not complex commands. He had word-finding difficulties, perseveration, and frontal release signs. Carotid ultrasound showed bilateral lesions, with 90% left internal carotid artery stenosis. A brain MRI showed a chronic infarct in the left frontal lobe. An FDG-PET scan showed focal left frontal hypoactivity, as well as diffuse left cerebral hypoactivity, including decreased activity in the left basal ganglia, thalamus, and the right cerebellum. Whole-body images showed no evidence of tumor recurrence or metastasis. Based on his progressive clinical symptoms and imaging studies, he was diagnosed with CBS.

3.2. Pathological findings

Pathological findings, including the distribution of infarcts, are summarized in Table 2. Arteriosclerotic small vessel disease was observed in two patients, particularly in arterioles of the basal ganglia. Alzheimer-related pathology was insignificant, and tau, α-synuclein, and TDP-43 pathology were not detected.

3.2.1. CBS-1

Macroscopically, the cerebral white matter had atrophy and discoloration, with gelatinous softening and partial cavitation. The white matter pathology was most marked in the frontal and parietal lobe, but also focally present in the temporal lobe and minimal in the occipital lobe. In the most affected areas, the white matter ischemic damage was so severe that it was nearly completely liquefied. The corpus callosum and internal capsule, especially the anterior limb, were also affected (Fig. 1A and B). There were dilated perivascular spaces, some cystic, in the thalamus and putamen. Histologically, tissue rarefaction in frontal white matter and internal capsule was associated with almost complete myelinated fiber loss and dense fibrillary gliosis (Fig. 1C). There were multiple foci of dystrophic calcification surrounded by lipid-laden macrophages in most severely affected white matter (Fig. 1D–F). The small vessels had arteriosclerotic hyalinosis, and some were completely obliterated by collagenosis (Fig. 1E, G). The white matter lesions had hypertrophic reactive astrocytes with GFAP (Fig. 1H). Similar changes were present in the internal capsule. The posterior limb of the internal capsule had severe degenerative changes with myelinated fiber loss, gliosis, granular foamy axonal spheroids, and dystrophic calcification. The cerebral peduncle, longitudinal fibers in the pontine base, medullary pyramid, and anterior corticospinal tract, but not lateral corticospinal tract, had severe atrophy with myelinated fiber loss and gliosis (Fig. 1I) consistent with unilateral Wallerian degeneration.

3.2.2. CBS-2

Macroscopically, there were small infarcts in the motor cortex and watershed region, as well as encephalomalacia in the left occipital pole (Fig. 1J–L). Basal ganglia showed a cystic softening in the lateral caudate and putamen, with the involvement of the anterior limb of the internal capsule (Fig. 1M). The right hemibrain had a large infarct in the superior parietal lobe and multiple small infarcts in the visual cortex and frontal watershed region. Microscopic examination revealed multiple small infarcts of varying histologic age, including cystic

Table 2
Pathological features and infarct distribution in patients with vascular CBS.

Pathologic features	CBS-1	CBS-2		CBS-3
Brain weight, g	920	1160		1400
Braak neurofibrillary tangle stage	0	I		II
Thal amyloid phase	0	0		0
Lewy body	–	–		–
TDP-43 proteinopathy	–	–		–
Arteriosclerosis/atherosclerosis	−/−	+/+		+/−
Cerebral amyloid angiopathy	–	–		–
Infarct distribution	**R**	**L**	**R****	**L**
Frontal watershed region	–	++	++	++
Motor cortex	–	++	–	+
Midfrontal gyrus	++*	+	–	–
Temporal lobe	++*	–	–	–
Parietal lobe	++*	–	++	–
Occipital lobe	+*	++	++	+
Periventricular white matter	++	+	–	++
Leukoencephalomalacia	+	+	–	+
Caudate	–	++	–	–
Putamen	++	++	–	–
Internal capsule	++	++	–	–
Globus pallidus	+	–	–	+
Basal nucleus	–	–	–	–
Thalamus	++	+	–	+
Subthalamic nucleus	–	–	–	–
Hippocampus	+	–	–	–
Cerebellum	+	+	–	–
Wallerian degeneration	**R**	**L**		**L**
Internal capsule	+	+		+
Cerebral peduncle	+	+		–
Longitudinal fibers in the pontine base	+	–		–
Medullary pyramids	+	–		–
Lateral corticospinal tract	–	NA		NA
Anterior corticospinal tract	+	NA		NA

+ indicates microinfarct and ++ indicates macroscopic infarct. * Infarcts in the white matter in these regions. ** This hemibrain is a frozen sample and assessed only macroscopically. Abbreviations: CBS, corticobasal syndrome; L, left; NA, not available for review; R, right.

subacute-to-chronic lesions, as well as acute infarcts. The pathology was especially marked in frontal lobe and watershed cortices (Fig. 1N and O). The centrum semiovale and periventricular white matter had marked rarefaction, loss of myelinated fibers, and perivascular collagenosis. There were cribriform changes and ischemic rarefaction, as well as both small and large infarcts in the caudate, putamen, internal capsule, and thalamus (Fig. 1P). The internal capsule and the corticopontine fibers of the cerebral peduncle showed advanced Wallerian degeneration. The cerebellum had multiple small infarcts affecting several folia in the hemisphere more than the vermis (Fig. 1Q).

3.2.3. CBS-3

Macroscopically, there were cortical infarcts in watershed regions and softening in the subjacent white matter, as well as partially cystic infarcts in the periventricular white matter in the left hemisphere (Fig. 1R). Histologically, there were many microscopic cortical infarcts of varying histologic age in the watershed region, motor cortex, and visual cortex (Fig. 1S and T). There was also subcortical white matter pathology and a large periventricular chronic infarct (Fig. 1U), with Wallerian degeneration of adjacent fiber tracts, including descending fibers in the internal capsule. The dorsal globus pallidus and anterior thalamus had chronic microinfarcts.

4. Discussion

This study investigated three patients with “vascular CBS”, who showed symptomatic small vessel disease with secondary corticospinal Wallerian degeneration without evidence of neurodegenerative pathology. Although small vessel disease may be a nonspecific radiographic finding, increasing evidence highlights the importance of small vessel disease in cognition [21], as well as gait and balance [22–24]. All patients met clinical criteria for CBS due to progressive asymmetric limb rigidity and limb apraxia. The frequency of vascular CBS was only 1.4% (3/217) in our cohort, but it might be under-represented due to selection bias.

To our knowledge, this is the first clinicopathological case series of vascular CBS. Some studies described vascular CBS based on MRI findings without pathological confirmation, leaving open the possibility that they had mixed vascular and degenerative pathologies [12,13]. Bhatia et al. reported two patients who presented with a progressive asymmetric syndrome of apraxia, rigidity, and dystonia [12]. They had chronic ischemic changes in the centrum semiovale and basal ganglia. One also had an infarct in the right insular cortex, while the other had bilateral infarcts in the pons. Subsequently, Kreisler et al. described five patients with progressive asymmetric rigidity and apraxia suggestive of CBS [13]. All patients had chronic ischemic changes in centrum semiovale. Basal ganglia were affected in four patients, and motor cortex was affected in three patients. Neuroimaging studies highlight brain regions associated with limb apraxia, a characteristic feature of CBS, to be frontal and parietal lobes, as well as parieto-frontal association fibers [25–28]. The thalamus and basal ganglia are also involved in a network of structures underlying praxis [29], likely through connections with frontal and parietal cortices [30]. Thus, patients with multiple infarcts in these brain regions may present with limb apraxia that can be mistaken for CBS, especially when signs and symptoms are asymmetric. In line with this, our pathological analyses showed small vessel disease with multiple infarcts in watershed regions, primary motor cortex, deep white matter, thalamus, and basal ganglia as the likely correlates of CBS.

Clinically silent small ischemic lesions in these anatomic regions may lead to disability over time due to secondary Wallerian degeneration. A study highlighting post-stroke upper limb spasticity showed that 33% of patients developed spasticity three months after a stroke, and another 17% developed spasticity at even later stages [9]. Furthermore, half of the patients with moderate spasticity progressed to severe spasticity [9]. This temporal profile resembles imaging studies of Wallerian degeneration [31]. Although early subtle changes may be evident using advanced imaging techniques, such as diffuse tensor imaging, within a few weeks after a stroke, Wallerian degeneration becomes obvious on routine T2-weighted images several weeks to months after the initial stroke [32].

In this study, all patients had an insidious onset and a progressive disease course. CBS-1 had multiple risk factors for cerebrovascular disease. Despite a lack of clinical history of hypertension, he had arteriosclerotic hyalinosis in small vessels. This finding is consistent with the fact that histopathological findings of small vessel disease can be seen in normotensive individuals and may imply other pathomechanism, such as endothelial damage [33]. Moreover, his symptoms were first noted by his relatives, suggestive of a clinically silent stroke. CBS-2 had asymmetric atrophy and ventricular dilation with hyperintense signal changes possibly due to Wallerian degeneration. Despite severe peripheral and ischemic heart disease, usual anticoagulant therapy was not possible. CBS-3 had onset of mild symptoms after open-heart surgery, a procedure with an increased risk of stroke. He showed progressive decline until his death, which was likely due to a combination of corticospinal Wallerian degeneration and additional clinically silent ischemic lesions. He was not eligible for anticoagulant therapy due to gastrointestinal bleeding. Although CBS-3 was not evaluated by a movement disorder neurologist, the other two patients were followed and diagnosed by movement disorder specialists. The clinical courses of these three patients suggest that multiple risk factors for cerebrovascular disease in a setting of suboptimal anticoagulant therapy should be red flags for vascular CBS.

Severe white matter lesions and the clinical triad of dementia, gait disturbance, and urinary incontinence in CBS-1 may raise a differential diagnosis of Binswanger's disease [34]; however, it is not associated with dystrophic calcification in white matter and is usually accompanied by multiple infarcts in the cerebral cortex and deep gray matter. Hereditary diffuse leukoencephalopathy with spheroids (HDLS) is another consideration that can present with CBS [35], but HDLS is not

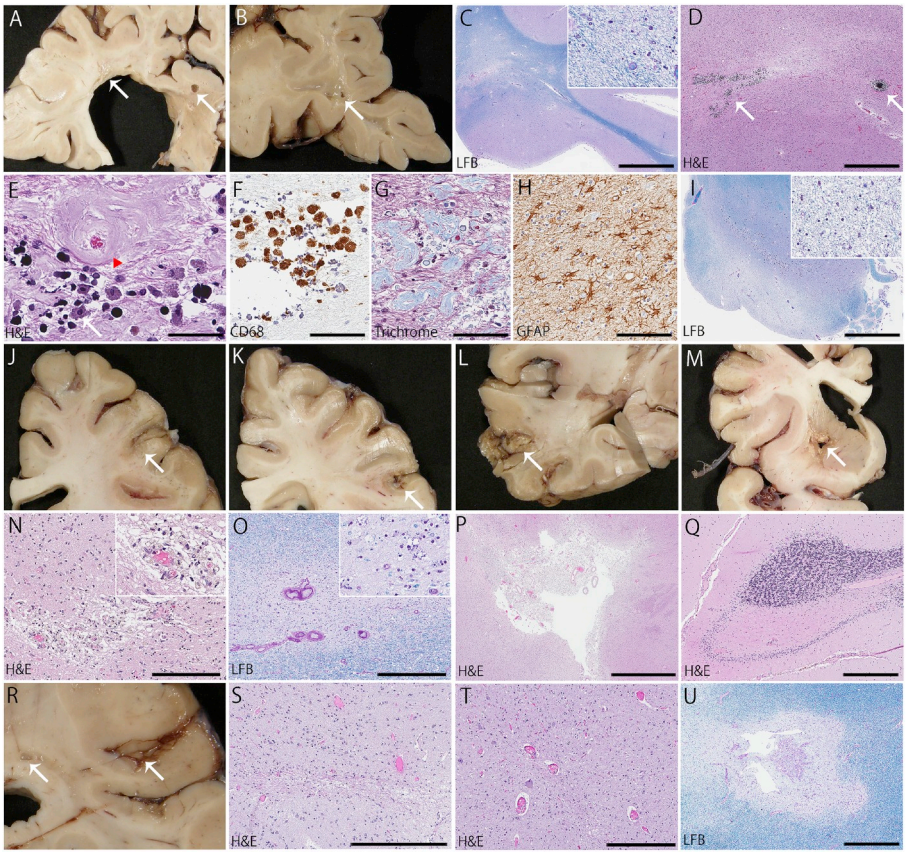

Fig. 1. Representative macroscopic and microscopic findings from CBS-1 (A–I), CBS-2 (J–Q), and CBS-3 (R–U). (A) The periventricular white matter is atrophic and nearly completely liquefied. A cystic infarct involves the putamen. (B) A white matter infarct in the frontal lobe. (C) Luxol fast blue stain shows myelin pallor in the white matter in the temporal lobe. (D) There are multiple foci of dystrophic calcification (arrows). There are lipid-laden macrophages (arrow in E) near the calcification, which are immunostained with CD68 (F). The small vessels have arteriosclerotic hyalinosis (arrowhead in E) clearly demonstrated on the Masson's trichrome stain (G). (H) The affected white matter lesions have reactive astrocytes. (I) Luxol fast blue stain reveals severe myelin loss in the entire cerebral peduncle. (J–O) CBS-2 has multiple infarcts in the motor cortex (J, N), watershed region (K, O), and occipital lobe (L). (M, P) A large cystic infarct involves caudate, putamen, and internal capsule. (Q) Multiple infarcts in cerebellar folia affecting granular cell layers and Purkinje cell layers. (R) CBS-3 has macroscopic infarcts in the watershed region (right arrow) and periventricular white matter (left arrow). (S–U) Cortical microinfarcts with linear scarring from the watershed region (S) and motor cortex (T), and a partially cystic infarct with myelin rarefaction in the periventricular white matter (U). D, E, N, P, Q, S, and T: hematoxylin-eosin stain; C, I, O, and U: Luxol fast blue stain; F: CD68-immunostain; G: Masson's trichrome stain; H: GFAP-immunostain. Bars: C, D, I, Q, S, and T = 500 μm; E = 50 μm; F, G, and H = 100 μm; N and O = 250 μm; P = 3 mm; U = 1 mm. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

associated with the type of ischemic damage detected in this case and often follows a frontotemporal distribution, without frank involvement of cortex and deep gray matter nuclei.

A limitation of this study is that clinical information was not based on standardized prospective or longitudinal clinical evaluations; therefore, some clinical findings might have been missed. Correlations between radiological and neuropathological findings were not evaluated in this study. Another limitation is the procedure of freezing one half of the brain and fixing the other half for neuropathology studies. Only the left hemibrain was available for neuropathological assessment in CBS-2, although the right hemibrain was likely more affected due to her left-predominant symptoms. To overcome this, the frozen right hemibrain was also sampled and observed to have multiple infarcts in the neocortices, which correlate with her left-predominant motor symptoms. The strength of our study was using autopsy-confirmed cases. A few patients with vascular CBS have been described in the literature; however, because of the lack of pathological confirmation, underlying CBD pathology cannot be completely excluded in these patients [12–15].

In summary, disruption of a network of structures underlying praxis, including frontal and parietal cortices, thalamus, basal ganglia, and white matter tracts between them, as well as corticospinal tract degeneration resulting from multiple infarcts can present with CBS. Our report highlight that despite a substantial time lag between a stroke and unexplained spasticity, high-risk patients may suffer clinically silent strokes and may warrant thromboembolic risk stratification and treatment. Although our patients did not display symmetric lower body parkinsonism, suggestive of vascular parkinsonism [5], the presence of unexplained asymmetric spasticity and dystonia in the absence of cortical sensory loss, bradykinesia or cogwheel rigidity may be red flags for vascular CBS. Follow-up neuroimaging studies should be applied in high-risk patients even without acute neurological deficits or apparent stepwise progression. The correct diagnosis and management of vascular CBS are important not only for clinical management but also for clinical research studies that do not have pathological confirmation.

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Author contributions

Shunsuke Koga: Conception and execution of the project; analysis and interpretation of data, writing of the manuscript.

Shanu F. Roemer: Interpretation of data; review and critique, writing of the manuscript.

Koji Kasanuki:Interpretation of data; review and critique.

Dennis W. Dickson: Conception and organization of the project; interpretation of data; review and critique, data collection.

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References

[1] N. Kouri, J.L. Whitwell, K.A. Josephs, R. Rademakers, D.W. Dickson, Corticobasal degeneration: a pathologically distinct 4R tauopathy, Nat. Rev. Neurol. 7 (5) (2011) 263–272.

[2] M.J. Armstrong, I. Litvan, A.E. Lang, T.H. Bak, K.P. Bhatia, B. Borroni, A.L. Boxer, D.W. Dickson, M. Grossman, M. Hallett, K.A. Josephs, A. Kertesz, S.E. Lee, B.L. Miller, S.G. Reich, D.E. Riley, E. Tolosa, A.I. Troster, M. Vidailhet, W.J. Weiner, Criteria for the diagnosis of corticobasal degeneration, Neurology 80 (5) (2013) 496–503.

[3] B.F. Boeve, A.E. Lang, I. Litvan, Corticobasal degeneration and its relationship to progressive supranuclear palsy and frontotemporal dementia, Ann. Neurol. 54 (Suppl 5) (2003) S15–S19.

[4] K. Kasanuki, K.A. Josephs, T.J. Ferman, M.E. Murray, S. Koga, T. Konno, N. Sakae, A. Parks, R.J. Uitti, J.A. Van Gerpen, N.R. Graff-Radford, Z.K. Wszolek, D.W. Dickson, Diffuse Lewy body disease manifesting as corticobasal syndrome: a rare form of Lewy body disease, Neurology 91 (3) (2018) e268–e279.

[5] P.M. FitzGerald, J. Jankovic, Lower body parkinsonism: evidence for vascular etiology, Mov. Disord. 4 (3) (1989) 249–260.

[6] J. Winikates, J. Jankovic, Vascular progressive supranuclear palsy, J. Neural Transm. Suppl. 42 (1994) 189–201.

[7] F. Alarcon, J.C. Zijlmans, G. Duenas, N. Cevallos, Post-stroke movement disorders: report of 56 patients, J. Neurol. Neurosurg. Psychiatry 75 (11) (2004) 1568–1574.

[8] B. Thanvi, N. Lo, T. Robinson, Vascular parkinsonism–an important cause of parkinsonism in older people, Age Ageing 34 (2) (2005) 114–119.

[9] K.H. Kong, J. Lee, K.S. Chua, Occurrence and temporal evolution of upper limb spasticity in stroke patients admitted to a rehabilitation unit, Arch. Phys. Med. Rehabil. 93 (1) (2012) 143–148.

[10] K.A. Josephs, T. Ishizawa, Y. Tsuboi, N. Cookson, D.W. Dickson, A clinicopathological study of vascular progressive supranuclear palsy: a multi-infarct disorder presenting as progressive supranuclear palsy, Arch. Neurol. 59 (10) (2002) 1597–1601.

[11] P.G. Glass, A.J. Lees, A. Bacellar, J. Zijlmans, R. Katzenschlager, L. Silveira-Moriyama, The clinical features of pathologically confirmed vascular parkinsonism, J. Neurol. Neurosurg. Psychiatry 83 (10) (2012) 1027–1029.

[12] K.P. Bhatia, M.S. Lee, J.O. Rinne, T. Revesz, F. Scaravilli, L. Davies, C.D. Marsden, Corticobasal degeneration look-alikes, Adv. Neurol. 82 (2000) 169–182.

[13] A. Kreisler, B. Mastain, F. Tison, G. Fenelon, A. Destee, [Multi-infarct disorder presenting as corticobasal degeneration (DCB): vascular pseudo-corticobasal degeneration?], Rev. Neurol. (Paris) 163 (12) (2007) 1191–1199.

[14] Y.D. Kim, J.S. Kim, E.S. Lee, D.W. Yang, K.S. Lee, Y.I. Kim, Progressive "vascular" corticobasal syndrome due to bilateral ischemic hemispheric lesions, Intern. Med. 48 (18) (2009) 1699–1702.

[15] Y. Miyaji, K. Koyama, T. Kurokawa, M. Mitomi, Y. Suzuki, Y. Kuroiwa, Vascular corticobasal syndrome caused by unilateral internal carotid artery occlusion, J. Stroke Cerebrovasc. Dis. 22 (7) (2013) 1193–1195.

[16] H. Braak, E. Braak, Neuropathological stageing of Alzheimer-related changes, Acta Neuropathol. 82 (4) (1991) 239–259.

[17] D.R. Thal, U. Rub, M. Orantes, H. Braak, Phases of A beta-deposition in the human brain and its relevance for the development of AD, Neurology 58 (12) (2002) 1791–1800.

[18] A.M. Liesinger, N.R. Graff-Radford, R. Duara, R.E. Carter, F.S. Hanna Al-Shaikh, S. Koga, K.M. Hinkle, S.K. DiLello, M.F. Johnson, A. Aziz, N. Ertekin-Taner, O.A. Ross, D.W. Dickson, M.E. Murray, Sex and age interact to determine clinicopathologic differences in Alzheimer's disease, Acta Neuropathol. 136 (6) (2018) 873–885.

[19] K. Gwinn-Hardy, N.D. Mehta, M. Farrer, D. Maraganore, M. Muenter, S.H. Yen, J. Hardy, D.W. Dickson, Distinctive neuropathology revealed by alpha-synuclein antibodies in hereditary parkinsonism and dementia linked to chromosome 4p, Acta Neuropathol. 99 (6) (2000) 663–672.

[20] S. Koga, N. Kouri, R.L. Walton, M.T.W. Ebbert, K.A. Josephs, I. Litvan, N. Graff-Radford, J.E. Ahlskog, R.J. Uitti, J.A. van Gerpen, B.F. Boeve, A. Parks, O.A. Ross, D.W. Dickson, Corticobasal degeneration with TDP-43 pathology presenting with progressive supranuclear palsy syndrome: a distinct clinicopathologic subtype, Acta Neuropathol. 136 (3) (2018) 389–404.

[21] E.L. Abner, P.T. Nelson, R.J. Kryscio, F.A. Schmitt, D.W. Fardo, R.L. Woltjer, N.J. Cairns, L. Yu, H.H. Dodge, C. Xiong, K. Masaki, S.L. Tyas, D.A. Bennett, J.A. Schneider, Z. Arvanitakis, Diabetes is associated with cerebrovascular but not Alzheimer's disease neuropathology, Alzheimers Dement 12 (8) (2016) 882–889.

[22] S.H. Kreisel, C. Blahak, H. Bazner, D. Inzitari, L. Pantoni, A. Poggesi, H. Chabriat, T. Erkinjuntti, F. Fazekas, J.M. Ferro, P. Langhorne, J. O'Brien, P. Scheltens, M.C. Visser, L.O. Wahlund, G. Waldemar, A. Wallin, M.G. Hennerici, Deterioration of gait and balance over time: the effects of age-related white matter change–the LADIS study, Cerebrovasc. Dis. 35 (6) (2013) 544–553.

[23] P. Mahlknecht, S. Kiechl, B.R. Bloem, J. Willeit, C. Scherfler, A. Gasperi, G. Rungger, W. Poewe, K. Seppi, Prevalence and burden of gait disorders in elderly men and women aged 60-97 years: a population-based study, PLoS One 8 (7) (2013) e69627.

[24] D. Pinter, S.J. Ritchie, F. Doubal, T. Gattringer, Z. Morris, M.E. Bastin, C.V.H.M. Del, N.A. Royle, J. Corley, S. Munoz Maniega, A. Pattie, D.A. Dickie, J. Staals, A.J. Gow, J.M. Starr, I.J. Deary, C. Enzinger, F. Fazekas, J. Wardlaw, Impact of small vessel disease in the brain on gait and balance, Sci. Rep. 7 (2017) 41637.

[25] K.M. Heilman, E. Valenstein, Clinical Neuropsychology, fifth ed., Oxford University Press, Oxford, 2012.

[26] K.Y. Haaland, D.L. Harrington, R.T. Knight, Neural representations of skilled movement, Brain 123 (Pt 11) (2000) 2306–2313.

[27] D.A. Kareken, F. Unverzagt, K. Caldemeyer, M.R. Farlow, G.D. Hutchins, Functional brain imaging in apraxia, Arch. Neurol. 55 (1) (1998) 107–113.

[28] B. Borroni, V. Garibotto, C. Agosti, S.M. Brambati, G. Bellelli, R. Gasparotti, A. Padovani, D. Perani, White matter changes in corticobasal degeneration syndrome and correlation with limb apraxia, Arch. Neurol. 65 (6) (2008) 796–801.

[29] P.P. Pramstaller, C.D. Marsden, The basal ganglia and apraxia, Brain 119 (Pt 1) (1996) 319–340.

[30] R.G. Gross, M. Grossman, Update on apraxia, Curr. Neurol. Neurosci. Rep. 8 (6) (2008) 490–496.

[31] Y. Inoue, Y. Matsumura, T. Fukuda, Y. Nemoto, N. Shirahata, T. Suzuki, M. Shakudo, S. Yawata, S. Tanaka, K. Takemoto, et al., MR imaging of Wallerian degeneration in the brainstem: temporal relationships, AJNR Am. J. Neuroradiol. 11 (5) (1990) 897–902.

[32] M.J. Kuhn, D.J. Mikulis, D.M. Ayoub, B.E. Kosofsky, K.R. Davis, J.M. Taveras, Wallerian degeneration after cerebral infarction: evaluation with sequential MR imaging, Radiology 172 (1) (1989) 179–182.

[33] J.M. Wardlaw, C. Smith, M. Dichgans, Mechanisms of sporadic cerebral small vessel disease: insights from neuroimaging, Lancet Neurol. 12 (5) (2013) 483–497.

[34] D.A. Bennett, R.S. Wilson, D.W. Gilley, J.H. Fox, Clinical diagnosis of Binswanger's disease, J. Neurol. Neurosurg. Psychiatry 53 (11) (1990) 961–965.

[35] Y. Baba, B. Ghetti, M.C. Baker, R.J. Uitti, M.L. Hutton, K. Yamaguchi, T. Bird, W. Lin, M.W. DeLucia, D.W. Dickson, Z.K. Wszolek, Hereditary diffuse leukoencephalopathy with spheroids: clinical, pathologic and genetic studies of a new kindred, Acta Neuropathol. 111 (4) (2006) 300–311.