Movement Disorders
CLINICAL PRACTICE
CLINICO-PATHOLOGICAL CASE

Pathologically Verified Corticobasal Degeneration Mimicking Richardson's Syndrome Coexisting with Clinically and Radiologically Shunt-Responsive Normal Pressure Hydrocephalus

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ABSTRACT: Background: Normal pressure hydrocephalus (NPH) manifests as gait instability, cognitive impairment, and urinary incontinence. This clinical triad of NPH sometimes occurs with ventriculomegaly in patients with neurodegenerative disease. Patients with pathologically verified neurodegenerative diseases, such as progressive supranuclear palsy (PSP), have received antemortem diagnoses of NPH.
Objectives: This study presents clinical and pathological features of a patient with pathologically verified corticobasal degeneration (CBD) coexisting with clinically shunt-responsive NPH.
Methods: We performed clinical, radiological, and pathological evaluations in a patient with CBD whose antemortem diagnosis was PSP Richardson's syndrome (PSP-RS) coexisting with shunt-responsive NPH.
Results: A 59-year-old woman developed bradykinesia and gait instability and then frequent falls, urinary incontinence, and supranuclear vertical gaze palsy followed. At 63 years of age, her gait disturbance and urinary incontinence had deteriorated rapidly, and cognitive impairment was disclosed. There were typical findings of NPH with ventriculomegaly and disproportionately enlarged subarachnoid space hydrocephalus as well as a 2-layer appearance with decreased and increased cerebral blood perfusion. Shunt placement ameliorated gait instability for more than 1 year and improved radiological indicators of NPH. However, atrophy of the midbrain progressed with time after transient increases in size. Although the antemortem diagnosis was probable PSP-RS, pathological evaluation verified CBD. There were severe discontinuities of the ependymal lining of the lateral ventricles and subependymal rarefaction and gliosis with tau-positive deposition.
Conclusions: Shunt surgery could ameliorate NPH symptoms in patients with 4-repeat tauopathies. Careful assessments of clinical findings are necessary to predict the benefits of shunts as a therapeutic option for patients with neurodegenerative diseases coexisting with NPH.

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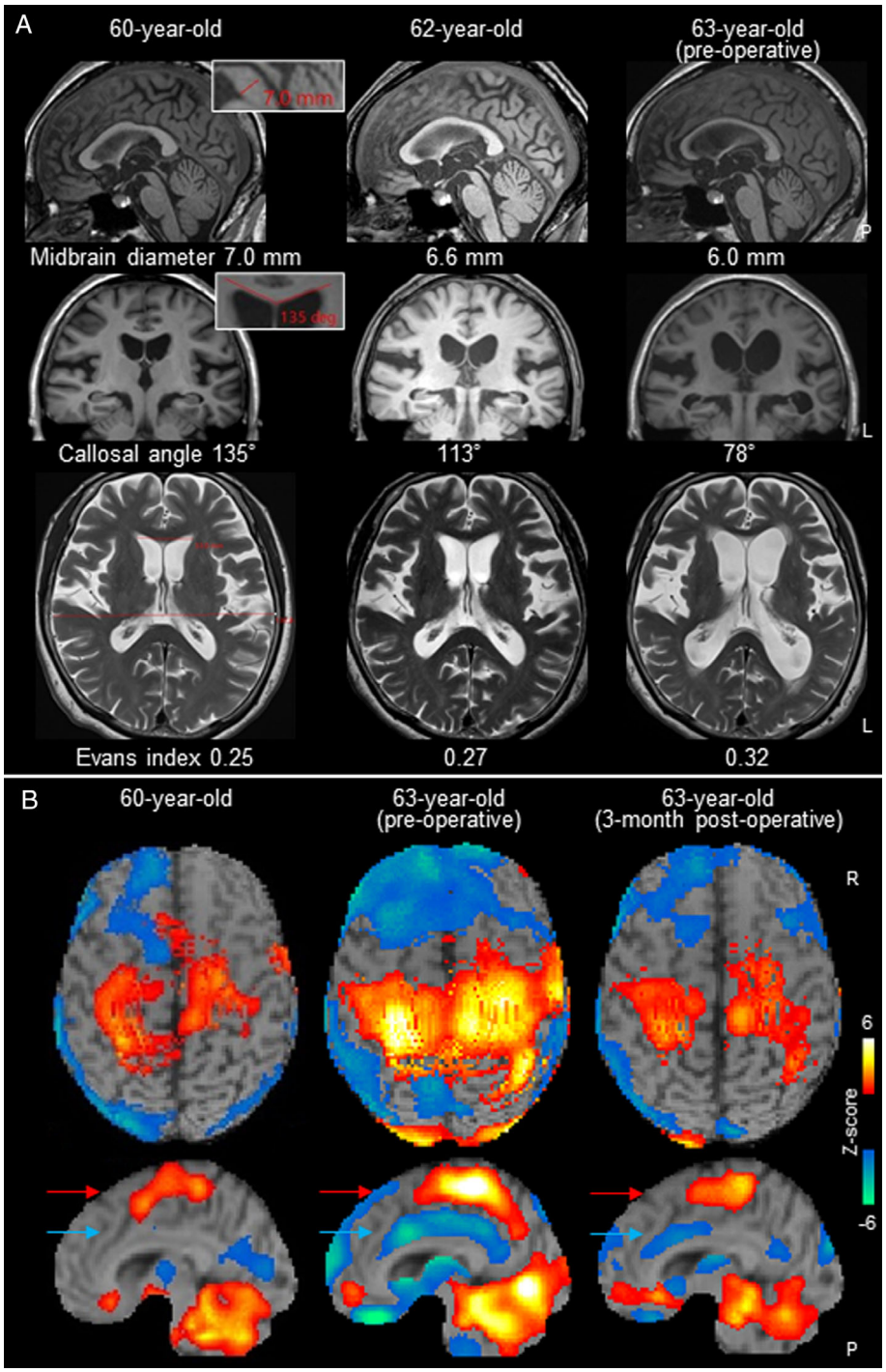


FIG. 1. Neuroradiological assessments at different time points. **(A)** The anteroposterior midbrain diameter, callosal angle, and Evans index on magnetic resonance imaging gradually decrease over time. **(B)** The 2-layer appearance consisting of decreased blood flow around the corpus callosum (blue arrows) and enhanced perfusion in areas surrounding the cingulate gyrus (red arrows) on brain perfusion single-photon emission computed tomography images using the easy Z-score imaging system program.

Normal pressure hydrocephalus (NPH) is characterized by gait instability, cognitive impairment, and urinary incontinence. Correct diagnosis of NPH in patients with these symptoms is critical because it can be treated by cerebrospinal fluid (CSF) drainage. A recent review stated that even in patients with apparent idiopathic NPH, diagnosing physicians should carefully consider the

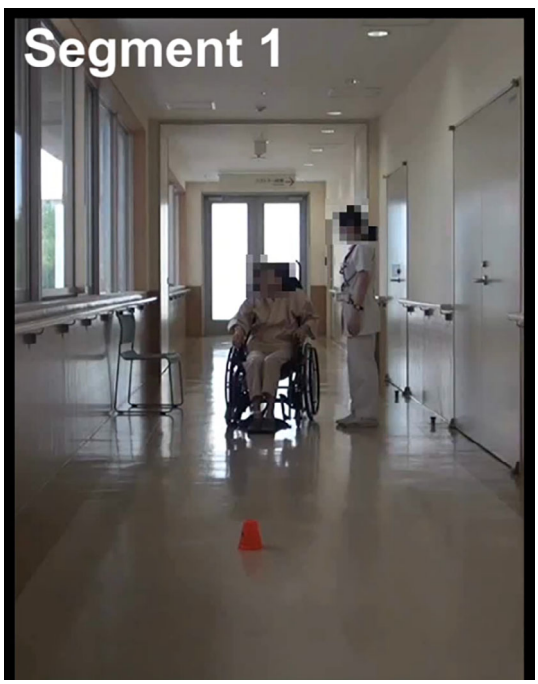
Video 1. The patient was unable to arise from a chair or walk without assistance all the time in the pre-operative assessment. Video content can be viewed at https://onlinelibrary.wiley.com/doi/10.1002/mdc3.13442

possibility of other neurodegenerative disorders, such as Alzheimer's disease (AD), dementia with Lewy bodies (DLB), and progressive supranuclear palsy (PSP). PSP is sometimes accompanied by ventriculomegaly, which is a radiological hallmark of NPH, and these patients are referred to as having "neurodegenerative NPH."[1] PSP Richardson's syndrome (PSP-RS) is the most common phenotype of PSP, and patients exhibit the clinical triad of NPH symptoms in addition to ventriculomegaly. Pathologically verified cases of PSP with an antemortem diagnosis of NPH have been reported and reviewed previously.[2] The clinical features of PSP can also manifest in patients with corticobasal degeneration (CBD), another 4-repeat tauopathy, in a condition known as "PSP syndrome."[3] Unlike cases of PSP with comorbid NPH, few articles have reported on pathologically verified CBD with comorbid NPH.[4]

Here, we report an autopsy case with pathologically verified CBD mimicking PSP-RS coexisting with clinically and radiologically verified shunt-responsive NPH.

Case Report

A 59-year-old Japanese woman developed bradykinesia and gait disturbance. She was evaluated at the outpatient clinic, where magnetic resonance imaging (MRI) of the brain revealed no abnormalities. She was diagnosed with Parkinson's disease and levodopa treatment was initiated. However, her bradykinesia gradually deteriorated, and she visited our hospital for further treatment. On neurological examination, she had bradykinesia, shuffling gait, and trivial muscle rigidity, but had no tremor or postural instability. Brain MRI demonstrated mild atrophy of the tegmentum in the midbrain (Fig. 1A, upper left). Dopamine transporter single-photon emission computed tomography (SPECT) with ^{123}I–N-ω-fluoropropyl-2β-carboxymethoxy-3β-(4-iodophenyl)nortropane showed diffusely reduced uptake in the bilateral striata (data not shown). ^{123}I–metaiodobenzylguanidine myocardial scintigraphy, performed to discriminate degenerative parkinsonism, showed normal uptake (data not shown). She exhibited no therapeutic response to levodopa for parkinsonism. Approximately 1 year later, she presented with freezing gait, frequent falls, and urinary incontinence, and a neurological examination revealed postural instability and slow saccades. At 3 years after the onset of symptoms, she presented with axial-predominant rigidity, supranuclear vertical gaze palsy, and bradyphrenia. Because her gait disturbance and urinary incontinence had deteriorated rapidly and because she required walking assistance (Video 1), especially during the 3 months before admission, she was admitted to our hospital for further examination.



Video 2. Segment 1: Three weeks after the shunt surgery. The patient could arise from a chair and walk with minimal assistance. Segment 2: Three months after the shunt surgery. The patient no longer required assistance to arise or walk. However, monitoring by a helper during the gait was needed because mild gait instability remained.
Video content can be viewed at https://onlinelibrary.wiley.com/doi/10.1002/mdc3.13442

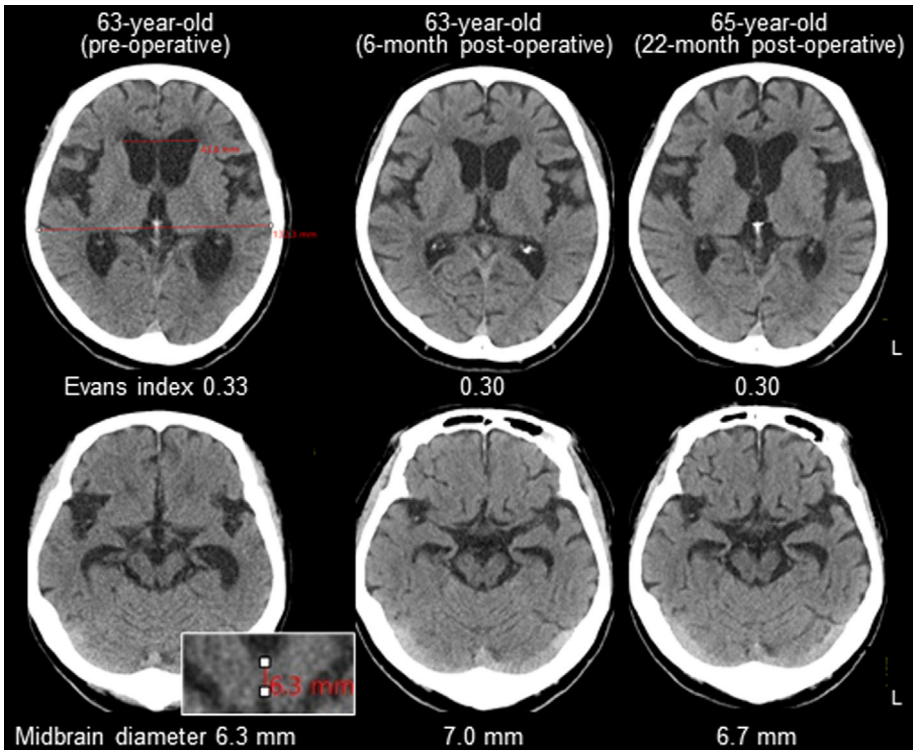


FIG. 2. Series of brain computed tomography images before and after shunt surgery. Ventriculomegaly is improved until the late stage of the disease (upper row). The anteroposterior midbrain diameter shows a transient improvement after shunt surgery; however, this deteriorates again at 22 months after surgery (lower row).

On admission, she was apathetic and wheelchair bound. Her speech was fluent but small and slow, and bradyphrenia was apparent. There were signs of frontal lobe dysfunction, including perseveration and grasp reflex. She showed severe cognitive impairment and scored 7/30 on the Mini-Mental State Examination and 1/18 on the Frontal Assessment Battery. The neurological examination also revealed axial-predominant parkinsonism, postural instability, oculomotor dysfunction with supranuclear vertical palsy and horizontal saccadic slowing, bilateral hyperreflexia, and mild left-hand clumsiness, but no evidence of myoclonus, dystonia, or alien hand syndrome. A brain MRI revealed progressive atrophy of the tegmentum in the midbrain and brain atrophy with enlargement of the ventricles and Sylvian fissures as well as high-convexity tightness (eg, disproportionately enlarged subarachnoid space hydrocephalus [DESH]; Fig. 1A). The anteroposterior diameter of the midbrain (MD), callosal angle (CA), and Evans index (EI) calculated from the brain MRI gradually decreased over time (Fig. 1A). Evaluation with ^{99m}Tc–ethyl cysteinate dimer SPECT (^{99m}Tc–ECD SPECT) revealed regional hypoperfusion in the bilateral frontal cortex and hyperperfusion in the bilateral convexity, and the easy Z-score imaging system revealed a 2-layer appearance consisting of decreased blood flow around the corpus callosum and enhanced perfusion in areas surrounding the cingulate gyrus, suggesting NPH (Fig. 1B).[5,6] Because the rapid clinical deterioration of gait instability, urinary incontinence, and neuroradiological findings was highly suggestive of NPH, we performed a large-volume lumbar puncture for CSF drainage. This enabled us to determine whether the patient with PSP had comorbid NPH. The opening pressure of CSF was normal (11 cmH_2O) with a slightly elevated level of CSF protein (57 mg/dl). After CSF drainage, the patient's gait instability and bradyphrenia were sufficiently improved to reduce the burden on caregivers. We discussed the possible prognosis with the patient and her family and explained that the benefits of CSF shunt placement could be transient and overwhelmed by the progression of PSP. Subsequently, we obtained informed consent for the lumbo-peritoneal (L-P) shunt procedure.

L-P shunt surgery was performed under general anesthesia with the Codman Certas programmable valve system (Johnson & Johnson K.K., Tokyo, Japan). The ventral catheter was inserted via the L3/L4 intervertebral space. The opening pressure of the valve was adjusted in the outpatient clinic. After the shunt surgery, the patient's gait instability, urinary incontinence, and bradyphrenia recovered over time. Her gait freezing was ameliorated, and she could walk by herself (Video 2). However, she required supervision because her postural instability did not

improve, resulting in frequent falls. At 3 months after the L-P shunt placement, her score on the PSP rating scale[7] had decreased from 65 before the surgery to 40. At 1.5 years after the shunt surgery, she could walk by herself for a short distance in the clinic. Her bradyphrenia had remitted by 6 months after the shunt surgery. However, 1 year after the surgery, she could not communicate verbally and constantly made incomprehensible groaning sounds. She continued to deteriorate gradually until dysphagia prevented her from eating enough, and she died at the age of 65 years, 6 years after the onset of the disease. Radiologically, brain computed tomography (CT) demonstrated that her ventriculomegaly and DESH persisted in improvement until the late stage of the disease (Fig. 2, upper row). Furthermore, ^{99m}Tc–ECD SPECT revealed that the 2-layer appearance had disappeared after the shunt surgery (Fig. 1B, right column). Although the anteroposterior MD calculated from the axial brain CT increased temporarily after the shunt surgery, it decreased again with the progression of PSP (Fig. 2, lower row). This radiological series of changes was consistent with the clinical features. Hence, the final clinical diagnosis was probable PSP-RS, according to the Movement Disorders Society Criteria for PSP,[8] concomitant with NPH.

Neuropathological Findings

The brain weighed 1129 grams and showed mild cerebral atrophy without laterality, mild atrophy of the frontal operculum (Fig. 3A), and dilated lateral ventricles with thinning of the corpus callosum (Fig. 3B) on gross examination at autopsy. There was atrophy at the level of the thalamus, subthalamic nucleus (STN), globus pallidus (GP), and tegmentum throughout the brain stem. Microscopic assessment showed severe neuronal loss with gliosis in the frontal lobes, especially in the precentral gyrus, accompanying ballooned neurons, astrocytic plaques (Fig. 3C), coiled bodies, and threads (Fig. 3D), without laterality of these tau-related pathological findings. Immunohistochemistry of these abnormal depositions revealed phosphorylated 4-repeat but not 3-repeat tau-positive depositions. These characteristics were also found in the STN, thalamus, GP, putamen, nucleus basalis of the Meynert, substantia nigra, locus coeruleus, pontine nucleus, and inferior olivary nucleus. In the cerebellar dentate nucleus, there was neuronal loss and gliosis accompanying threads and pretangles, but the Purkinje cells were preserved. Interestingly, there were severe discontinuities of the ependymal lining of the lateral ventricles and subependymal rarefaction and gliosis

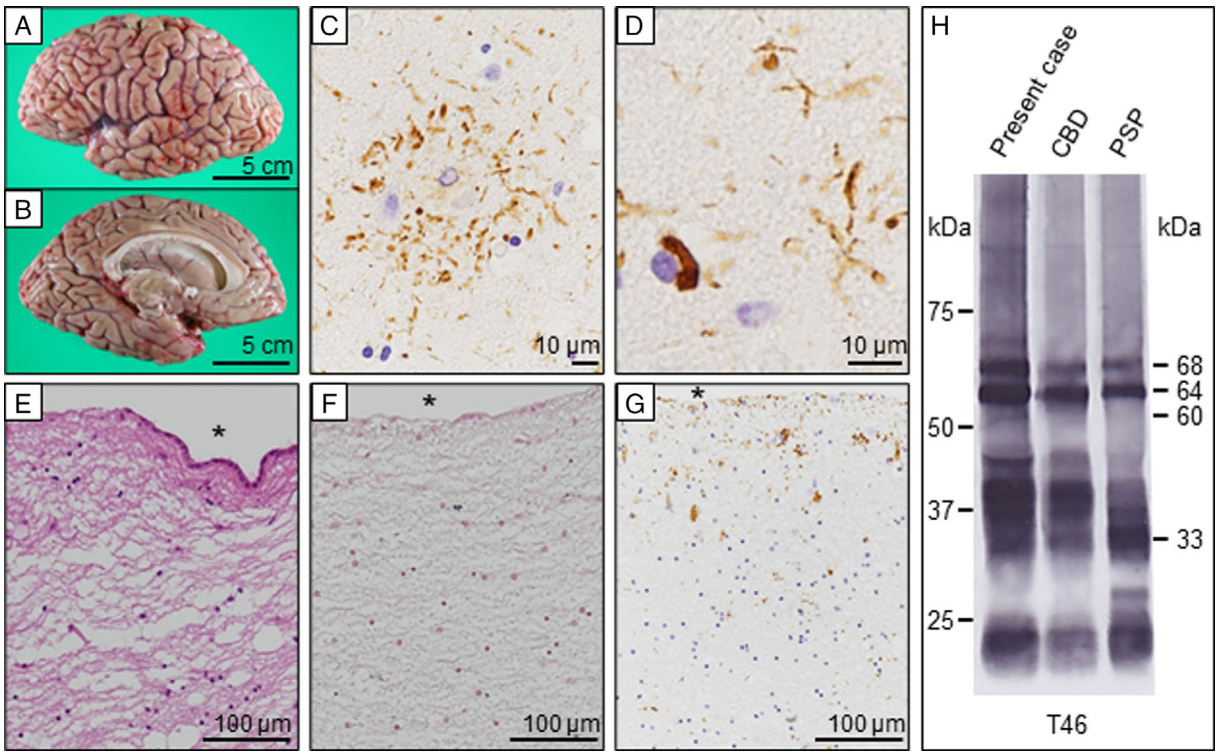


FIG. 3. Neuropathological findings. (**A,B**) Mild cerebral atrophy of the frontal operculum and dilated lateral ventricles with thinning of the corpus callosum. (**C**) Tau-positive astrocytic plaque and (**D**) coiled bodies and threads in the precentral gyrus (immunohistochemistry using an AT8 antibody). (**E,F**) Discontinuities of the ependymal lining, subependymal rarefaction, and gliosis (E, hematoxylin and eosin staining; F, Gallyas-Braak staining). (**G**) Tau-positive deposition in the subependymal region (immunohistochemistry using an AT8 antibody). Asterisks represent the lateral ventricle. (**H**) Western blot analysis of sarkosyl-insoluble tau from the brain probed using a T46 antibody. CBD, corticobasal degeneration; PSP, progressive supranuclear palsy.

(Fig. 3E,F). Immunohistochemistry revealed tau-positive deposition in the subependymal region (Fig. 3G). Western blot analysis of sarkosyl-insoluble tau from the brain showed a major doublet of 68 and 64 kDa with predominant ≈37 kDa fragments, similar to that of CBD, but different from that of PSP, in which the ≈33 kDa fragments are predominant (Fig. 3H).[9] These histopathological and biochemical findings were consistent with the pathological features of CBD.

Discussion

Differentiating NPH from other neurological disorders remains challenging for 3 main reasons. First, the classic triad of symptoms of NPH is nonspecific, and these symptoms could develop even in the normal aged population. Second, ventriculomegaly, which is the radiological hallmark of NPH, occurs in various neurodegenerative disorders, and DESH, another radiological feature of NPH, may be misinterpreted as cortical atrophy.[10] Third, most neurodegenerative disorders have no definitive diagnostic tests except for pathological evaluations, which require an invasive procedure, and NPH does not have any specific neurological hallmarks. A literature review of NPH studies indicated that the benefits of shunt implantation in patients with an initial diagnosis of idiopathic NPH persisted in only 32% of patients at 36 months, leading to a revised diagnosis in more than 25% of patients (AD, DLB, and PSP).[1] To avoid the misdiagnosis of NPH and other neurodegenerative disorders, especially in patients with PSP who exhibit the clinical triad of NPH symptoms, radiological biomarkers with MRI are suggested.[11,12] Distinguishing NPH from neurodegenerative disorders is necessary to avoid shunt-related complications such as infection and headache because shunt surgery is not likely to have beneficial effects in patients with neurodegenerative disorders.

However, our case highlighted the therapeutic potential of shunt placement for neurodegenerative diseases that are comorbid with NPH. Serial MRI of our case demonstrated the deterioration of NPH findings, such as CA and EI (Fig. 1A), as well as the manifestation of the 2-layer appearance upon ^{99m}Tc–ECD-SPECT (Fig. 1B). This occurred at 63 years of age, which was the point at which our patient showed a rapid progression of gait instability. Furthermore, our patient showed clinically and radiologically verified responses to the shunt surgery in terms of NPH symptoms and radiological abnormalities (Figs. 1B and 2, Video 2). In particular, gait instability was ameliorated until 1.5 years after the surgery. Thus, our case demonstrates the utility of the ventricular shunt as a symptomatic therapy in patients with a neurodegenerative disease concomitant with NPH, even though the indication should be carefully considered (eg, response to large-volume CSF drainage, both morphological and functional radiological findings). Informed consent that the benefits of CSF shunt placement could be transient and overwhelmed by the progression of neurodegenerative disease must be obtained.

Although the clinical diagnosis of our case was probable PSP-RS according to the recent criteria of PSP,[8] pathological evaluation revealed CBD pathology. This demonstrates the difficulty in distinguishing PSP from CBD without a pathological examination.[13] Considering that the neuropathology of CBD is accurately predicted antemortem in less than 50% of patients,[3] some reported cases of PSP with comorbid NPH might have CBD neuropathology because most of these cases lacked pathological evaluation. Previously, only 1 case of pathologically verified CBD with presumed NPH was reported in a case-series study,[4] and the clinical course and pathological evaluation of that patient was not described in detail. To our knowledge, this is the first detailed clinicopathological case report of pathologically verified CBD mimicking PSP-RS with coexisting NPH. Our pathological evaluation revealed discontinuities of the ependymal lining of the lateral ventricles as well as subependymal rarefaction and gliosis with tau-positive deposition. Although the role of subependymal tau-positive deposition in NPH is not known, it could contribute to the pathogenesis of NPH in terms of tauopathy. The glymphatic system enables the outflow of CSF, as mediated by astrocytes expressing water channel aquaporin-4, and patients with AD or idiopathic NPH exhibit reduced CSF clearance.[14] The delayed enhancement and decreased clearance of the intrathecally injected contrast agent in patients with idiopathic NPH demonstrated by glymphatic MRI technique suggests that impaired glymphatic function contributes to pathomechanism of idiopathic NPH.[15] Astroglial dysfunction caused by the deposition of abnormal tau in the CBD brain could be associated with glymphatic system disturbances, which could eventually lead to excess CSF accumulation. However, further research is required to determine the triggers for NPH in patients with neurodegenerative disease, because not all patients with tauopathy or AD manifest NPH.

In conclusion, NPH can coexist with 4-repeat tauopathies, such as CBD in our case and PSP, and shunt surgery for NPH can ameliorate symptoms, especially impaired gait. Careful assessments of clinical symptoms and radiological findings are expected to facilitate the identification of neurological comorbidities and predict the benefits of a shunt, resulting in improved patient care. As impaired CSF clearance is considered 1 of the mechanisms of NPH, abnormal tau-induced dysfunction of astrocytes is a possible pathogenic element and thus may be a therapeutic target for neurodegenerative diseases that are comorbid with NPH.

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Author Roles

(1) Research Project: A. Conception, B. Organization, C. Execution; (2) Manuscript Preparation: A. Writing of the First Draft, B. Review and Critique.

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Y.T.: 1B, 1C, 2B

Disclosures

Ethical Compliance Statement: Ethical approval from institutional review board was not required for this work because this is a case report. Written informed consent was obtained from the patient's next-of-kin for donation for diagnostic and research purposes, and publication of the clinicopathological details and/or clinical images. We confirm that all authors have read the Journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines.

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