Pearls & Oy-sters: Idiopathic Normal Pressure Hydrocephalus With Synucleinopathy

Diagnosis and Treatment

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Pearls

- Idiopathic normal pressure hydrocephalus (iNPH) is characterized by the classic triad of gait disturbance, urinary incontinence, and cognitive impairment in the presence of ventriculomegaly without known risk factors for communicating hydrocephalus.
- Shunt surgery is indicated for patients with iNPH who respond to the removal of CSF.

MORE ONLINE

Oy-sters

- Striatal dopaminergic deficit on dopamine transporter (DAT) scan can be seen in patients with iNPH.
- Abnormal DAT imaging may be seen in patients with an unfavorable long-term outcome of shunt surgery.
- For patients with iNPH with clinical features suggesting synucleinopathy such as REM sleep behavior disorder, DAT scan could be considered to identify concurrent synucleinopathy before shunt surgery, even in cases with initial response to high-volume lumbar puncture.

A 70-year-old man presented with a 2-year history of progressive disturbances of gait, balance, control of urination, and cognition. He also had mild constipation, but he did not have other symptoms suggesting dysautonomia, such as orthostatic dizziness, syncope, or sweating abnormalities. He had no history of head trauma, meningitis, or intracranial hemorrhage. Neurologic examination revealed postural instability, bradykinesia, and subtle limb rigidity. His gait was slow with reduced arm swing and stride length (mean stride length 20.1 cm, walking speed 20.3 cm/s) (video 1). Motor and sensory functions were normal. Deep tendon reflexes were normal, and there was no ataxia or pathologic reflexes. He scored 22 on the Mini-Mental State Examination (MMSE). Routine laboratory tests were normal. Brain MRI showed enlarged lateral ventricles (Evans index 0.32) and disproportionately enlarged subarachnoid space hydrocephalus (DESH) (figure).¹ He was diagnosed with iNPH and underwent daily lumbar puncture (LP) with removal of 50 mL of CSF for 2 consecutive days. Routine CSF analysis was unremarkable. After LP, mean stride length and walking speed increased to 76.6 cm and 72.4 cm/s, respectively (video 2). Ventriculoperitoneal shunt (VPS) surgery was recommended but refused by the patient and his family. Interestingly, the improvement of gait was sustained for several months. The mean stride length and walking speed were 76.0 cm and 71.3 cm/s, respectively, after 7 months of LP (video 3).

The patient was lost to follow-up. Two years after the initial visit, he again presented with aggravated gait. He was taking levodopa/carbidopa (100/25 mg) 3 times a day that was prescribed elsewhere. His family also reported that he exhibited dream enactment behavior. He had no history of visual hallucination or fluctuation of cognition. The mean stride length and

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walking speed were 13.0 cm and 12.1 cm/s, respectively (video 4). He scored 24 on the MMSE. MRI findings of enlarged lateral ventricles and DESH were similar to the previous MRI (figure). After he underwent LP with removal of 50 mL of CSF, the mean stride length and walking speed increased to 46.6 cm and 31.7 cm/s, respectively (video 5). ^{18}F -N-3-fluoropropyl-2 β -carboxymethoxy-3 β -(4-iodophenyl)-nortropane (FP-CIT) PET showed reduced DAT uptake bilaterally throughout the striatum, including the caudate nucleus and the putamen (figure).

The dose of levodopa/carbidopa was increased to 250/50 mg 3 times a day. The mean stride length and walking speed slightly increased to 53.4 cm and 41.6 cm/s, respectively (video 6). Gait was still improved 1 month after LP (mean stride length 48.5 cm, walking speed 44.6 cm/s) (video 7). Although gait improved after high-volume LP, the parkinsonian features on neurologic examination, dream enactment behavior, and reduced striatal DAT uptake on FP-CIT PET support an underlying synucleinopathy in this patient.

Discussion

Normal pressure hydrocephalus is characterized by the classic triad of gait disturbance, urinary incontinence, and cognitive impairment in the presence of ventriculomegaly, which is ameliorated by the removal of CSF.² The diagnosis of iNPH is made by excluding known risk factors for communicating hydrocephalus including meningitis, traumatic brain injury, subarachnoid hemorrhage, and brain irradiation.² Shunt surgery is indicated for patients with iNPH who respond to the removal of CSF.² It has been shown that patients with iNPH present with normal presynaptic DAT binding in the striatum.³ However, although our patient's gait disturbance was improved by LP with CSF removal, FP-CIT PET showed reduced DAT binding throughout the striatum, including the caudate nucleus and the putamen. Given that 25% of patients with iNPH who underwent shunt surgery were revealed to have a diagnosis other than iNPH,⁴ our patient might have a concomitant neurodegenerative disorder affecting presynaptic nigrostriatal neurons. His dream enactment behavior suggests underlying synucleinopathy such as Parkinson disease or dementia with Lewy bodies.⁵ In addition, the degree of improvement in gait after the second LP was not as robust as that resulting from the first LP, which could be a sign of concurrent neurodegeneration in our patient.

It has been recently reported that striatal dopaminergic deficit on DAT scan was common (46.7%) in patients with iNPH⁶; furthermore, 1 year after VPS, 6 (42.9%) of 14 patients with reduced striatal DAT binding had a favorable outcome, whereas 13 (81.3%) of 16 patients with normal striatal DAT binding had a favorable outcome. Similarly, it has been shown that reduced striatal DAT binding was common (46.2%) in patients with iNPH, and 3 (60.0%) of 5 patients with reduced striatal DAT binding had a favorable postshunt outcome, whereas 6 (85.7%) of 7 patients with normal striatal DAT binding had a favorable postshunt outcome.⁷ DAT imaging studies also indicated that the caudate nucleus was affected more than the putamen in patients with iNPH.^{7,8} A recent study indicated that 8 patients with iNPH who had additional neurologic diseases had persistent improvement, whereas 10 (43.5%) of 23 patients without concomitant neurologic diseases had persistent improvement.⁴ In addition, a patient with iNPH comorbid with progressive parkinsonism was found to have concomitant synucleinopathy with REM sleep behavior disorder (RBD) and decreased DAT binding in the striatum 3 years after shunt surgery.⁹ Considering these results, the long-term outcome of shunt surgery might not be favorable in patients with iNPH with concomitant synucleinopathy. Therefore, it could be recommended for patients with iNPH with clinical features suggesting synucleinopathy such as RBD to undergo DAT imaging before shunt surgery and discuss the long-term outcome of the surgery with neurologists and neurosurgeons.

It has been shown that the improvement of gait after the removal of CSF rarely persists for more than a few days in

patients with iNPH.² However, the response after CSF removal sometimes could be sustained, as in our patient, for a few months.¹⁰ Although the exact mechanism is not clear, the prolonged response might be attributed to the elasticity of the ventricular wall.¹⁰ After LP, the total resistance and subsequently the tensile strength of the ventricular wall are decreased.^{e1} If the tensile strength of the ventricular wall is decreased further after LP, the effect of LP could be profound and prolonged.^{e2} Repeated removal of CSF every 7 months was reported to prevent decline in gait performance in patients with iNPH ineligible for shunt surgery.^{e3}

Larger studies are needed to investigate the prevalence of concomitant synucleinopathy and to determine safe and effective treatment options.

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Name	Location	Contribution
Sang-Won Han, MD	Seoul National University College of Medicine and Seoul National University Bundang Hospital	Design and conceptualization of the study, analysis and interpretation of the data, drafting and revising of the manuscript
Young Ho Park, MD, PhD	Seoul National University College of Medicine and Seoul National University Bundang Hospital	Design and conceptualization of the study, critical revision of manuscript for important intellectual content, study supervision
Nayoung Ryoo, MD	Seoul National University College of Medicine and Seoul National University Bundang Hospital	Acquisition of data and analysis and interpretation
Kitae Kim, MD	Seoul National University College of Medicine and Seoul National University Bundang Hospital	Acquisition of data
Jung-Min Pyun, MD	Seoul National University College of Medicine and Seoul National University Bundang Hospital	Analysis and interpretation
SangYun Kim, MD, PhD	Seoul National University College of Medicine and Seoul National University Bundang Hospital	Design and conceptualization of the study, critical revision of the manuscript for important intellectual content

References

1. Ambarki K, Israelsson H, Wählin A, Birgander R, Eklund A, Malm J. Brain ventricular size in healthy elderly: comparison between Evans index and volume measurement. *Neurosurgery*. 2010;67:94-99.
2. Williams MA, Relkin NR. Diagnosis and management of idiopathic normal-pressure hydrocephalus. *Neurol Clin Pract*. 2013;3:375-385.
3. Tatsch K, Poepperl G. Nigrostriatal dopamine terminal imaging with dopamine transporter SPECT: an update. *J Nucl Med*. 2013;54:1331-1338.
4. Espay AJ, Da Prat GA, Dwivedi AK, et al. Deconstructing normal pressure hydrocephalus: ventriculomegaly as early sign of neurodegeneration. *Ann Neurol*. 2017;82:503-513.
5. Postuma R, Gagnon J, Vendette M, Fantini M, Massicotte-Marquez J, Montplaisir J. Quantifying the risk of neurodegenerative disease in idiopathic REM sleep behavior disorder. *Neurology*. 2009;72:1296-1300.
6. Broggi M, Redaelli V, Tringali G, et al. Normal pressure hydrocephalus and parkinsonism: preliminary data on neurosurgical and neurological treatment. *World Neurosurg*. 2016;90:348-356.
7. Allali G, Garibotto V, Mainta IC, Nicastro N, Assal F. Dopaminergic imaging separates normal pressure hydrocephalus from its mimics. *J Neurol*. 2018;265:2434-2441.
8. Lee JY, Park SB, Lee M, Ju H, Im K, Kwon KI. Detailed visual assessment of striatal dopaminergic depletion in patients with idiopathic normal pressure hydrocephalus: unremarkable or not? *BMC Neurol*. 2020;20:277.
9. Shimada H, Shimada Y. Progressive parkinsonism three years after shunt surgery in a patient with idiopathic normal pressure hydrocephalus. *Intern Med*. 2020;59:2183-2186.
10. Lim T, Yong S, Moon S. Repetitive lumbar punctures as treatment for normal pressure hydrocephalus. *Eur Neurol*. 2009;62:293-297.

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