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

Author(s):
Sang-Won Han, MD; Young Ho Park, MD, PhD; Nayoung Ryoo, MD; Kitae Kim, MD; Jung-Min Pyun, MD; SangYun Kim, MD, PhD

Corresponding Author:
Young Ho Park
kumimesy@snubh.org

Neurology® Published Ahead of Print articles have been peer reviewed and accepted for publication. This manuscript will be published in its final form after copyediting, page composition, and review of proofs. Errors that could affect the content may be corrected during these processes.
Affiliation Information for All Authors: Sang-Won Han, MD, Department of Neurology, Seoul National University College of Medicine and Seoul National University Bundang Hospital, Republic of Korea; Young Ho Park, MD, PhD, Department of Neurology, Seoul National University College of Medicine and Seoul National University Bundang Hospital, Republic of Korea; Nayoung Ryoo, MD, Department of Neurology, Seoul National University College of Medicine and Seoul National University Bundang Hospital, Republic of Korea; Kitae Kim, MD, Department of Neurology, Seoul National University College of Medicine and Seoul National University Bundang Hospital, Republic of Korea; Jung-Min Pyun, MD, Department of Neurology, Seoul National University College of Medicine and Seoul National University Bundang Hospital, Republic of Korea; SangYun Kim, MD, PhD, Department of Neurology, Seoul National University College of Medicine and Seoul National University Bundang Hospital, Republic of Korea

Contributions:
Sang-Won Han: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data; Study concept or design; Analysis or interpretation of data
Young Ho Park: Drafting/revision of the manuscript for content, including medical writing for content; Study concept or design; Additional contributions: Study supervision; critical revision of manuscript for important intellectual content
Nayoung Ryoo: Major role in the acquisition of data; Analysis or interpretation of data
Kitae Kim: Major role in the acquisition of data
Jung-Min Pyun: Analysis or interpretation of data
SangYun Kim: Study concept or design; Additional contributions: Critical revision of the manuscript for important intellectual content

Number of characters in title: 86

Abstract Word count: 1189

References: 10

Figures: 1

Tables: 0


Acknowledgements: This work was supported by the National Research Foundation of Korea grant (No. 2020R1C1C1013718).

Study Funding: The authors report no targeted funding

Disclosures: The authors report no disclosures relevant to the manuscript.
Pearls

1. 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.

2. Shunt surgery is indicated for iNPH patients who respond to the removal of CSF.

Oysters

1. Striatal dopaminergic deficit on dopamine transporter (DAT) scan can be seen in patients with iNPH.

2. Abnormal DAT imaging may be seen in patients with an unfavorable long-term outcome of shunt surgery.

3. For iNPH patients 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.

Case report

A 70-year-old man presented with a 2-year history of progressive disturbances of gait, balance, control of urination, and cognition. He also complained of 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) (Supplemental video 1,http://links.lww.com/WNL/B387). 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 idiopathic normal pressure hydrocephalus (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 (Supplemental video 2,http://links.lww.com/WNL/B388). 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 (Supplemental video 3,http://links.lww.com/WNL/B389).

Since then, 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) three 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 walking speed were 13.0 cm and 12.1 cm/s, respectively (Supplemental video 4,http://links.lww.com/WNL/B390). He scored 24 on the MMSE. The MRI findings of enlarged lateral ventricles and DESH were similar to the previous MRI scan (Figure 1). 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 (Supplemental video
Furthermore, $^{18}$F-N-3-fluoropropyl-2β-carboxymethoxy-3β-(4-iodophenyl)nortropane (FP-CIT) PET showed reduced dopamine transporter (DAT) uptake bilaterally throughout the striatum, including the caudate nucleus and the putamen (Figure 1). The dose of levodopa/carbidopa was increased to 250/50 mg three times a day. Then, the mean stride length and walking speed slightly increased to 53.4 cm and 41.6 cm/s, respectively (Supplemental video 6,http://links.lww.com/WNL/B392). His gait was still improved one month after LP (mean stride length 48.5 cm, walking speed 44.6 cm/s) (Supplemental video 7,http://links.lww.com/WNL/B393). Although gait improved after high-volume lumbar puncture, the parkinsonian feature on neurological 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. The diagnosis of iNPH is made by excluding known risk factors for communicating hydrocephalus including meningitis, traumatic brain injury, subarachnoid hemorrhage, and brain irradiation. Shunt surgery is indicated for iNPH patients who respond to the removal of CSF. It is known that patients with iNPH present with normal presynaptic DAT binding in the striatum. However, although our iNPH 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 iNPH patients who underwent shunt surgery were revealed to have a diagnosis other than iNPH, 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. 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.

Recently, Broggi et al. reported that the striatal dopaminergic deficit on DAT scan was common (46.7%) in patients with iNPH; 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, Allali et al. found that reduced striatal DAT binding was also common (46.2%) in iNPH patients, and 3 (60.0%) of 5 patients with reduced striatal DAT binding had a favorable post-shunt outcome, whereas 6 (85.7%) of 7 patients with normal striatal DAT binding had a favorable post-shunt outcome. DAT imaging studies also indicated that the caudate nucleus was affected more than the putamen in patients with iNPH. Considering comorbidities, Espay et al. investigated the outcome 3 years after shunt surgery, and none of the 8 patients with iNPH who had additional neurological diseases had persistent improvement, whereas 10 (43.5%) of 23 patients without concomitant neurological diseases had persistent improvement. In addition, a case 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. Considering these results, the long-term outcome of shunt surgery might not be favorable in iNPH patients with concomitant synucleinopathy. Therefore, it could be recommended for iNPH patients 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 is also known that the improvement of gait after the removal of CSF rarely persists
for more than a few days in patients with iNPH. However, the response after CSF removal sometimes could be sustained, as in our patient, for a few months. Although the exact mechanism is not clear, the prolonged response might be attributed to the elasticity of the ventricular wall. After LP, the total resistance and subsequently the tensile strength of the ventricular wall are decreased. If the tensile strength of the ventricular wall is decreased further after LP, the effect of LP could be profound and prolonged. Repeated removal of CSF every 7 months was reported to prevent decline in gait performance in iNPH patients ineligible for shunt surgery.

Additional studies need to be conducted, with a larger sample size, to investigate the prevalence of concomitant synucleinopathy in iNPH patients as well as to determine which treatment option is safe and effective.
Figure 1. Brain MRI and FP-CIT PET of the patient

(A) Axial FLAIR image at the initial visit shows a widened third ventricle with a span of 1.2 cm (blue line). (B) Axial FLAIR image at the initial visit shows measurement of Evans index: the diameter of the frontal horns (red line) was 4.4 cm, the widest brain diameter (green line) was 13.6 cm, and the Evans index was 0.32 (C) Coronal T1-weighted image at 2 years after the initial visit shows widened sylvian fissures and enlarged temporal horn of lateral ventricle. (D) Axial FP-CIT PET image shows reduced dopamine transporter uptake bilaterally throughout the striatum, including the caudate nucleus and the putamen. (E) Bar graph shows the change in mean stride length and walking speed during the clinical course.

Abbreviations: FLAIR: Fluid-attenuated inversion recovery; FP-CIT: $^{18}$F-N-3-fluoropropyl-2β-carboxymethoxy-3β-(4-iodophenyl)-nortropane; LP: Lumbar puncture
## Appendix 1: Authors contributions

<table>
<thead>
<tr>
<th>Name</th>
<th>Location</th>
<th>Contribution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sang-Won Han, MD</td>
<td>Seoul National University College of Medicine and Seoul National University Bundang Hospital</td>
<td>Design and conceptualization of the study, analysis and interpretation of the data, drafting and revising of the manuscript</td>
</tr>
<tr>
<td>Young Ho Park, MD, PhD</td>
<td>Seoul National University College of Medicine and Seoul National University Bundang Hospital</td>
<td>Design and conceptualization of the study, critical revision of manuscript for important intellectual content, study supervision</td>
</tr>
<tr>
<td>Nayoung Ryoo, MD</td>
<td>Seoul National University College of Medicine and Seoul National University Bundang Hospital</td>
<td>Acquisition of data and analysis and interpretation</td>
</tr>
<tr>
<td>Kitae Kim, MD</td>
<td>Seoul National University College of Medicine and Seoul National University Bundang Hospital</td>
<td>Acquisition of data</td>
</tr>
<tr>
<td>Jung-Min Pyun, MD</td>
<td>Seoul National University College of Medicine and Seoul National University Bundang Hospital</td>
<td>Analysis and interpretation</td>
</tr>
<tr>
<td>SangYun Kim, MD</td>
<td>Seoul National University</td>
<td>Design and conceptualization of</td>
</tr>
<tr>
<td>PhD</td>
<td>College of Medicine and Seoul National University Bundang Hospital</td>
<td>the study, Critical revision of the manuscript for important intellectual content</td>
</tr>
</tbody>
</table>
Video 1 - http://links.lww.com/WNL/B387

Video 2 - http://links.lww.com/WNL/B388

Video 3 - http://links.lww.com/WNL/B389

Video 4 - http://links.lww.com/WNL/B390

Video 5 - http://links.lww.com/WNL/B391

Video 6 - http://links.lww.com/WNL/B392

Video 7 - http://links.lww.com/WNL/B393

References


Supplemental Data

Supplemental video 1. Video recording of gait before lumbar puncture with CSF removal at the initial visit

Supplemental video 2. Video recording of gait after lumbar puncture with CSF removal at the initial visit

Supplemental video 3. Video recording of gait 7 months after the initial visit

Supplemental video 4. Video recording of gait before lumbar puncture with CSF removal at the revisit (2 years after the initial visit)

Supplemental video 5. Video recording of gait after lumbar puncture with CSF removal at the revisit

Supplemental video 6. Video recording of gait after lumbar puncture with CSF removal and increasing dose of levodopa/carbidopa at the revisit

Supplemental video 7. Video recording of gait 1 month after the revisit
Data available from Dryad (e-References. e1, e2, e3): doi:10.5061/dryad.66t1g1k11
Pearls & Oy-sters: Idiopathic Normal Pressure Hydrocephalus With Synucleinopathy: Diagnosis and Treatment
Sang-Won Han, Young Ho Park, Nayoung Ryoo, et al.
Neurology published online April 30, 2021
DOI 10.1212/WNL.0000000000012099

This information is current as of April 30, 2021

<table>
<thead>
<tr>
<th>Updated Information &amp; Services</th>
<th>including high resolution figures, can be found at: <a href="http://n.neurology.org/content/early/2021/04/30/WNL.0000000000012099.citation.full">http://n.neurology.org/content/early/2021/04/30/WNL.0000000000012099.citation.full</a></th>
</tr>
</thead>
<tbody>
<tr>
<td>Subspecialty Collections</td>
<td>This article, along with others on similar topics, appears in the following collection(s): All Cognitive Disorders/Dementia <a href="http://n.neurology.org/cgi/collection/all_cognitive_disorders_dementia">http://n.neurology.org/cgi/collection/all_cognitive_disorders_dementia</a> Cerebrospinal Fluid <a href="http://n.neurology.org/cgi/collection/cerebrospinal_fluid">http://n.neurology.org/cgi/collection/cerebrospinal_fluid</a> Hydrocephalus <a href="http://n.neurology.org/cgi/collection/hydrocephalus">http://n.neurology.org/cgi/collection/hydrocephalus</a> PET <a href="http://n.neurology.org/cgi/collection/pet">http://n.neurology.org/cgi/collection/pet</a></td>
</tr>
<tr>
<td>Permissions &amp; Licensing</td>
<td>Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at: <a href="http://www.neurology.org/about/about_the_journal#permissions">http://www.neurology.org/about/about_the_journal#permissions</a></td>
</tr>
<tr>
<td>Reprints</td>
<td>Information about ordering reprints can be found online: <a href="http://n.neurology.org/subscribers/advertise">http://n.neurology.org/subscribers/advertise</a></td>
</tr>
</tbody>
</table>

Neurology © is the official journal of the American Academy of Neurology. Published continuously since 1951, it is now a weekly with 48 issues per year. Copyright © 2021 American Academy of Neurology. All rights reserved. Print ISSN: 0028-3878. Online ISSN: 1526-632X.