Normal Pressure Hydrocephalus

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Introduction

Normal pressure hydrocephalus (NPH) is a syndrome that was first described in 1965 by Hakim and Adams [1]. It is characterized by the clinical triad of memory impairment, gait disturbance, and urinary incontinence, accompanied by the presence of normal cerebrospinal fluid (CSF) pressure on lumbar puncture and the radiologic finding of enlarged cerebral ventricles [1].

NPH is now separated into two clinical categories: idiopathic NPH (iNPH) and secondary NPH, when the ventricular enlargement develops as a sequela of a known disease process. Typical conditions that can cause secondary NPH include subarachnoid hemorrhage, infectious meningitis, intracranial surgery, and other inflammatory or neoplastic processes. Surgical ventricular shunting is considered the standard-of-care treatment for many of these patients. However, response to ventricular shunting is variable and can be short-lived, with significant risks including complication rates up to 38% [2, 3].

Etiology

Many theories have been proposed to explain the mechanisms underlying the development of iNPH, although the exact etiology remains unclear. It is likely that iNPH is multifactorial, resulting from impaired CSF dynamics in combination with congenital and vascular etiologies.

The most widely accepted theory is that iNPH results from disordered CSF circulation, comprised of an imbalance among CSF production, circulation, and reabsorption [4]. Over time, CSF volume increases with a compensatory increase in ventricular volume to maintain normal intracranial pressure. Any increased pulse pressure on the ventricular

New York Presbyterian-Weill Cornell, Department of Radiology, New York, NY, USA e-mail: gcc9004@med.cornell.edu walls can result in a "waterhammer" effect, disturbing the paracentral fibers of the corticospinal tracts and contributing to the gait disturbance described in iNPH [5].

More recently, it has been proposed that alterations in glymphatic pathways can contribute to iNPH. The glymphatic system is a clearance pathway by which CSF flows through the periarterial space into the brain parenchyma, is transported via aquaporin-P4 water channels into the interstitial space, and flows through the perivenous space before draining into the cervical lymphatic system [6]. A defective glymphatic system can result in impaired CSF clearance and buildup of toxic metabolic products, including amyloid-β peptides and tau protein, potentially leading to the development of iNPH and Alzheimer's disease (AD) [7, 8]. Recent studies using imaging to examine the glymphatic system in iNPH patients found evidence for delayed clearance from the subarachnoid space and entorhinal cortex, as well as ventricular reflux towards the periventricular white matter, which may contribute to the development of dementia in iNPH [5, 7, 9–11].

In addition to evidence for altered CSF dynamics and clearance in iNPH, the possibility of a genetic cause of iNPH was proposed by Portenoy et al., who described the occurrence of the syndrome in two siblings [12]. Other studies have reported that more than 10% of patients with iNPH have a large head size, which supports the idea that developmental factors may impact the development of hydrocephalus [13, 14]. More recently, copy number variations in SFMBT1, a gene encoding a protein of the choroid plexus endothelium involved in CSF secretion, have been reported in iNPH patients [15].

Vascular disease has also been reported to alter CSF dynamics and contribute to the development of iNPH [16]. Severity of small vessel disease, especially periventricular white matter changes, have particularly been associated with higher prevalence of iNPH [17] and a less favorable prognosis [18].

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Epidemiology and Clinical Presentation

Approximately 10% of the 50 million people worldwide living with dementia suffer from iNPH [11]. iNPH is a disease of older individuals, with prevalence increasing with age; more than 2% of people aged 65 to 79 have the disease, compared to almost 9% of people 80 years and older [19].

Clinical diagnosis is often based on the presence of the classic iNPH triad of symptoms:

- Gait impairment: Gait dysfunction is typically the initial symptom of iNPH and is characterized by a "magnetic" or apraxic gait, which occurs in the absence of primary sensorimotor deficits, cerebellar dysfunction, or involuntary movements. Rather, it is believed to result from difficulty integrating sensory information about the position of the body and properly executing motor function [20, 21]. However, gait abnormalities occur in 20% of individuals older than the age 75, so it is important to exclude other causes [6, 22].
- 2. Cognitive impairment and dementia: The cognitive impairment seen with iNPH is commonly described as an executive dysfunction that manifests as slow processing, difficulty with problem solving, and memory deficits with poor retrieval but relatively intact recognition memory [21, 23]. These symptoms can overlap with neurode-generative disorders, including parkinsonian syndromes, AD, dementia with Lewy bodies, and vascular dementia. Furthermore, many patients with iNPH have comorbid AD and vascular dementia, making diagnosis challenging [24].
- 3. Urinary urgency and incontinence: Urgency and frequency are the most common urinary symptoms and may occur with or without incontinence [25]. Patients are usually aware of the urinary urge before incontinence occurs. Since bladder symptoms are very common among the elderly, incontinence occurs in 38% of women and 18% of men in this age group [26, 27], other causes should also be considered in patients with suspected iNPH.

Commonly, an unexplained, symmetric gait disturbance is the primary symptom of iNPH. Although cognitive impairment and urinary symptoms are part of the iNPH triad and are frequently present, the complete triad is not required to suspect the disorder [21]. Of note, the remainder of the neurologic examination, besides these three symptoms, is typically normal.

According to the American-European and Japanese NPH evidence-based guidelines for diagnosis and management, patients suspected to have iNPH can be classified into probable, possible, and unlikely categories. Possible iNPH is defined by (a) being older than 60 years old, (b) having one or more symptoms of the clinical triad, (c) MR evidence of ventricular dilatation and a narrow CSF space at the vertex, (d) CSF pressure < 200 mmH₂O with a normal CSF cell count and protein level (a) no other disease that may account

count and protein level, (e) no other disease that may account for the symptoms, and (f) having had no other previous illnesses that can cause ventricular dilatation. A patient is considered to have probable iNPH if the patient meets the criteria for possible iNPH and has a positive spinal tap test [28, 29].

CSF Tap Test and CSF Biomarkers

The CSF tap test consists of testing gait and cognitive function both before and after the drainage of approximately 40-50 milliliters of CSF via a lumbar puncture. Since the single tap CSF tap test has a low sensitivity, ranging from 26 to 61%, a negative result cannot be used to exclude patients from surgery. If there is a high clinical suspicion for iNPH despite a negative CSF tap test, one alternative diagnostic test is a repeated tap test; this involves performing lumbar punctures on three consecutive days and draining at least 30-40 milliliters of CSF each time. Another alternative would be to perform continuous external lumbar drainage (ELD) for 3-5 days, with a minimum of 150 ml CSF drained daily. ELD has a high positive predictive value of 80-100% and fairly high sensitivity of 50-100%. Since ELD best simulates the effect of definitive shunt surgery, it is considered the most effective test for identifying shuntresponsive cases according to the 2005 International iNPH guidelines [30]. However, ELD also requires hospital admission and is associated with higher complication rates, including meningitis, subdural hematoma, and nerve root inflammation [31, 32].

CSF biomarkers have not yet been proven to be useful in confirming the diagnosis of iNPH. Some studies comparing CSF biomarkers in patients with iNPH and AD have reported low A β 42 levels in iNPH; however, CSF tau was reported to be both normal and increased [33–36]. A challenge with using CSF biomarkers in this disease group is that many patients may have concomitant iNPH and AD pathology, resulting in overlap of CSF biomarkers.

Imaging Features

Conventional MRI

Currently, MRI is the imaging method of choice for assessing iNPH and has been incorporated into the international and Japanese diagnostic guidelines [37]. Importantly, iNPH is a communicating hydrocephalus, so any sign of CSF obstruction needs to be excluded. Three of the cardinal neuroimaging findings of iNPH are as follows:

- The Evans index (EI) is the most commonly used measure for ventricular enlargement, first described in 1942. It is calculated by taking the ratio of the widest width of the frontal horns of the lateral ventricles and the widest width of the intracranial compartment on an axial image (Fig. 38.1) [38]. International guidelines propose an EI of greater than 0.3 is suggestive of iNPH, although its specificity is questioned [39, 40]. Yamada et al. developed the "z-Evans index" with additional measurements of the frontal horns of the lateral ventricle, resulting in higher accuracy in predicting patient response to a tap test [41].
- 2. The callosal angle (CA) is defined by two lines tangentially aligned with the medial walls of the lateral ventricular walls on coronal images. iNPH patients commonly have a CA that is less than 90 degrees, and this has been found to be a good predictor of shunt response [42–44]. When combined with an EI of greater than 0.3, iNPH can be discriminated from AD with a sensitivity and specificity of 97% and 94%, respectively [45].
- 3. The MR sign described as "disproportionately enlarged subarachnoid space hydrocephalus" (DESH) is character-

ized by narrowed sulci in the midline at the high convexity, combined with enlarged Sylvian fissures and ventricular dilation (Fig. 38.1). The evaluation of this sign is performed on a coronal image at the level of the posterior commissure. This sign is highly associated with the clinical triad of iNPH, is not typically seen in the setting of brain atrophy, and is a good predictor of response to shunt surgery [46–50].

Volumetric analysis of the hippocampi can also aid in differentiating iNPH from AD, since hippocampal atrophy is not a prominent feature in iNPH (Fig. 38.2) [51]. A few papers have also described an upward bowing of the corpus callosum, although this can be seen in many forms of hydrocephalus and is not specific to iNPH (Fig. 38.3) [52, 53].

A less commonly used sign is the presence of a prominent CSF flow void, extending through the cerebral aqueduct to the obex of the fourth ventricle [5]. It is believed to be related to the hyperdynamic flow seen in iNPH. During systole, arterial pressure forces blood flow into the brain, putting pressure on already enlarged ventricles and leading to hyperdynamic CSF flow. Because of this increased flow, the walls of the third ventricle, which normally bow inward,



Fig. 38.1 Axial (a) and coronal (b) T2-weighted fluid-attenuated inversion recovery MR images showing two commonly used MR features of idiopathic normal pressure hydrocephalus (iNPH). The Evans index (a) can be calculated by dividing the maximum width of the frontal horns of the lateral ventricles (D_1) by the maximum width of the

intracranial compartment (D_2). An Evans' index of 0.3 or higher is suggestive of ventriculomegaly, as seen in iNPH. The MR sign "disproportionately enlarged subarachnoid space hydrocephalus" (DESH) is show in (**b**), in which there is narrowing of the sulci at the high convexities, but prominent Sylvian fissures



Fig. 38.2 Coronal T1-weighted MR image (**a**) demonstrating preservation of hippocampal volumes (**a**, curved arrows), which can help differentiate normal pressure hydrocephalus from Alzheimer's disease. Fused 18F-FDG PET/T1-weighted axial MR image (**b**) demonstrates

cortical hypometabolism in the frontal and parietal lobes (straight arrows). Patterns of hypometabolism in these patients can be heterogeneous



Fig. 38.3 Sagittal T1-weighted MR image (**a**) demonstrating upward bowing of the corpus callosum (curved arrow), which can be seen in many forms of hydrocephalus, including normal pressure hydrocepha-

lus. Sagittal 18F-FDG PET image (**b**) demonstrates cortical hypometabolism in the frontal lobes (straight arrow)

become parallel or even bow outward. If these patients are not shunted, they will eventually develop atrophy [5].

CSF Flow Studies with MRI

Newer MR imaging techniques have intrinsic flow compensation, which masks the prominent CSF flow void that has been previously described in iNPH patients [5]. As a result, phase-contrast cine MR imaging has emerged as a promising technique to evaluate CSF flow in iNPH patients and to appropriately select candidates for ventriculoperitoneal shunting [54]. Using this technique, many MR imaging systems can calculate the volume of CSF flowing in a craniocaudad direction during systole and caudocranial during diastole. Aqueductal CSF stroke volume (ACSV) is the commonly used measure for the average volume of CSF passing through the aqueduct of Sylvius during the cardiac cycle. ACSV is increased in iNPH patients and decreases after successful shunting [54–57]. Bradley et al. found that patients who respond to shunting for iNPH have at least twice the ACSV of healthy elderly patients [5]. Although the reproducibility and reliability of ACSV values for prognosis in iNPH have been questioned [58], [59] phase-contrast MR imaging is often combined with a high-volume CSF tap test or ELD to assess whether or not to perform shunt surgery [5, 60, 61].

Advanced MR Imaging

In the last decade, several studies have explored the utility of advanced imaging techniques, such as diffusion tensor imaging (DTI) and resting state functional MRI (rs-fMRI), in the setting of iNPH. Although some positive correlations have been described in the literature, a clear advantage to using these advanced imaging techniques, either for diagnosis of iNPH or prediction of shunt response, is not evident [55, 62–67].

Higher mean diffusivity (MD) and lower fractional anisotropy (FA) in the corpus callosum and subcortical white matter of the bilateral temporal, parietal, and occipital lobes have been reported in iNPH patients, differentiating them from other neurodegenerative diseases. These measures are believed to result from the mechanical force exerted by the enlarged lateral ventricles onto the surrounding tissues and are also reportedly associated with worse gait performance [68–70]. Another paper combined the FA values in the internal capsule with the Evans index, achieving a diagnostic specificity of 100% for iNPH [62]. Ivkovic et al. used DTI as a supplementary test to distinguish iNPH from AD, Parkinson's disease, and Lewy body dementia, achieving a sensitivity of 86% and specificity of 96% [71]. Other papers have combined MD in the superior thalamic radiations with ventricular volumes or alterations in corticospinal tract microstructure to discriminate among iNPH, AD, and agematched healthy controls [64, 72]. Further validation in larger cohorts and correlation with clinical outcomes are warranted.

Studies using rs-fMRI have shown some promise. For example, reduced interhemispheric, temporal, anterior/posterior cingulate, and precuneus functional connectivity contributed to the accurate classification of iNPH versus controls [73–75]. Ogata et al. found that interhemispheric functional connectivity was most relevant to iNPH classification, which suggests that disruption of corpus callosum fibers due to ventricular enlargement may explain the clinical triad of iNPH [76]. However, more validation is needed since the spatial location and direction of the functional connectivity were poorly consistent across studies [75].

Positron Emission Tomography (PET)

¹⁸F-FDG-PET may be useful in the evaluation of a patient for iNPH by excluding other neurodegenerative diseases, specifically AD [77]. However, some patients could have iNPH and comorbid AD; in studies in which the brain was biopsied at the time of shunt placement for iNPH, about 30% of patients had concomitant AD pathology [78].

The utility of ¹⁸F-FDG-PET as a specific biomarker for iNPH is unclear. The pattern of hypometabolism can be heterogeneous, with many studies reporting hypometabolism globally or in several cortical regions (Figs. 38.2, 38.3, and 38.4) [77, 79]. Recent studies have also suggested that hypometabolism in the basal ganglia and thalami may be diagnostic [80, 81].

PET imaging with an amyloid tracer has also been used in the setting of iNPH. Mostly, this is used to determine whether there is concomitant AD pathology, in the form of betaamyloid plaques. Some have suggested that shunt surgery may be less effective in individuals with concomitant AD. However, a study of 15 patients who underwent shunt surgery found that 13 benefited from the surgery and 7 of those that benefited had positive amyloid PET scans [82]. As a result, there is no clear evidence for PET imaging for amyloid plaques in this cohort.

Finally, some studies have used ¹⁵O-H₂O-PET to measure cerebral blood flow in iNPH, finding a global reduction compared to healthy controls. However, studies that evaluated changes in blood flow before and after shunt surgery did not find a significant difference [83–87].



Fig. 38.4 Stereotactic surface projections of the brain from an 18F-FDG PET study demonstrating patchy areas of cortical hypometabolism involving the frontal, parietal, and temporal lobes, more

pronounced on the left. There is preserved FDG uptake in the occipital lobes and cerebellum

Other Imaging Modalities

Computerized tomographic cisternography is not recommended for clinical examination, due to its low specificity. However, recently, radionuclide cisternography with SPECT/ CT has been proposed as an important exam for the evaluation of iNPH [88, 89]. In one study, almost 90% of patients with a positive cisternography study showed clinical improvement after shunt surgery, which suggests that radionuclide cisternography may be superior to measurement of the CA and CSF flow in predicting response to surgical shunting [89].

Brain perfusion SPECT may also be diagnostic in identifying increased midline, high convexity perfusion with decreased Perisylvian fissure perfusion, termed the "convexity apparently hyperperfusion" (CAPPAH) sign [46, 90]. This sign was also confirmed to be useful in a multicenter SPECT study, which demonstrated relatively increased perfusion areas in the high convexity region with severely reduced relative CBF around the corpus callosum and in the Perisylvian region [91].

Treatment

iNPH is one of the few reversible causes of dementia, with treatment relying on efficient surgical diversion of CSF via shunt placement. Up to 10% of patients with dementia may have NPH and therefore may be treatable by shunting. Shunts are usually placed in the lateral ventricle or in the lumbar subarachnoid space and can have one of three different drainage points. The most common drainage site is the peritoneum, known as a ventriculoperitoneal shunt (VPS). Two other types of shunts, ventriculopleural and ventriculoatrial shunts, terminate in the pleural space and the internal jugular vein, respectively. The last type, the lumboperitoneal (LP) shunt, is placed in the lumbar intradural space and drains into the peritoneum. While VPS is the most widely used approach in North America and Europe, LP shunts predominates in Japan and other parts of Asia. Nevertheless, both have been shown to be effective for iNPH treatment [92].

The best response to shunting occurs early in the disease process, when gait disturbance is the primary symptom. In an unblinded randomized controlled trial of iNPH patients who underwent immediate LP shunt versus delayed treatment, only 5% of the delayed group showed clinical improvement at 3 months compared with over 65% of the treated group [93]. Later in the disease process, when dementia is evident, symptoms are less likely to improve with a mean chance of significant improvement of 30–50% [94, 95]. Nevertheless, it has been estimated that only 10% to 20% of patients with iNPH receive appropriate shunting, probably due to difficulties in diagnosing iNPH and the morbidity and mortality associated with shunt surgery [96].

Shunt complications can be significant and include subdural hematomas and effusions, infections, seizures, focal neurologic deficits, shunt malfunction, and death. Twenty percent of patients require additional surgery, and 6% develop permanent neurologic deficits or death [3].

Endoscopic third ventriculostomy (ETV) has been pursued as an alternative approach to shunting in iNPH. However, thus far, outcomes have not been favorable, so ETV is not currently recommended for treatment of iNPH [97].

Nonsurgical pharmacological approaches to managing hydrocephalus have been tried since 1924 using diuretics [98]. Acetazolamide, a carbonic anhydrase inhibitor, has also been studied to manage iNPH. It has been shown to reduce the production of CSF and interstitial edema by inhibiting the carbonic anhydrases present within the choroid plexus and preventing aquaporin-based water conductance via signaling pathways. Ivkovic et al. found improvement in clinical symptoms in a small iNPH cohort, but research is ongoing [96]. Therefore, shunting still remains the main treatment option [98].

Conclusion

iNPH is one of the few reversible causes of dementia in the elderly and can be appropriately treated with shunt surgery, especially if identified early. The precise cause of iNPH remains unclear, although altered CSF dynamics likely play a role. The classic clinical triad consists of gait disturbance, urinary incontinence, and cognitive impairment. A CSF tap test and MRI findings help to confirm the diagnosis. PET imaging can be used to assess the likelihood of a concomitant neurodegenerative disease, such as AD. Ultimately, more research needs to be done to more specifically diagnosis iNPH and better predict who will respond to surgical shunting.

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