



Addressing the Devil Within: Normal Pressure Hydrocephalus—A Narrative Review

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Abstract

Normal pressure hydrocephalus (NPH) is the most frequently occurring form of hydrocephalus among adults. It is characterized clinically by the classical triad, called Hakim's triad, comprising gait issues, cognitive impairment, and urinary problems. NPH may be primary or idiopathic (iNPH) or secondary. Characteristic neuroimaging features occur, which are vital to diagnosis. Diagnostic criteria in the form of Japanese guideline and Congress of Neurological Surgeons 2005 guidelines have been devised, and broadly, are based on a constellation of clinical and neuroimaging features, in association with cerebrospinal fluid (CSF) testing. CSF tap test, extended lumbar drainage, and CSF infusion tests are invasive diagnostic tests. CSF tap test and extended lumbar drainage are used to demonstrate clinical reversibility with CSF drainage, and patients who demonstrate this are candidates for CSF shunting. However, due to the low negative predictive value of these tests, potential response to shunting cannot be negated among patients who do not respond to CSF drainage. Various shunting procedures are used for treatment, including ventriculoperitoneal, lumboperitoneal, and ventriculoatrial shunts. Endoscopic third ventriculostomy has also been attempted with limited success. Among the clinical features, gait abnormalities are most responsive to shunting. Persistent long-term response to shunting has been reported. Patients need to be meticulously followed up after the shunting procedure, to assess clinical and neuroimaging response, and detect possible shunt-related complications, especially CSF over-drainage. Early treatment is associated with better prognosis, and it is crucial to recognize and treat this condition before the development of severe symptoms.

Keywords

- hydrocephalus
- CSF tap test
- ventriculoperitoneal shunts
- Evans' index

Introduction

Normal pressure hydrocephalus (NPH) is known to be the commonest cause of hydrocephalus in the adult population. The condition was first described by Hakim and Adams in 1957 in Columbia.^{1,2} The term NPH is used to denote the classical triad of gait abnormalities, cognitive dysfunction, and urinary urgency and incontinence. It is linked to

expansion of cerebral ventricles without an increase in cerebrospinal fluid (CSF) pressure.³ This clinical triad is popularly known as Hakim's triad or Adam's triad.

Classification

NPH is classified as primary or secondary NPH. Primary or idiopathic NPH (iNPH) occurs in the absence of known

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precipitants. Secondary NPH occurs because of complications of other disease processes. These include prior subarachnoid hemorrhage, meningitis, and head injury. Expansion of ventricles occurs in the absence of obstruction to CSF flow, and in association with any combination of triad symptoms, including gait abnormality, urinary urgency/incontinence, and cognitive deterioration. The diagnosis of NPH is important to make because of the possibility of effective treatment, in the form of CSF shunting.

Epidemiology

The usual age at onset of NPH is usually in the sixth and seventh decades. The estimated incidence of NPH ranges between 0.2 and 5.5/100,000 per year.⁴ There is an age-wise increase in prevalence, which ranges from 3.3 per 100,000 for people between 50 and 59 years of age. Among people in the age group of 60 to 69 years, the incidence is reported to be 49.3/100,000. Among individuals above 70 years of age, it is 181.7/100,000. Among the elderly, it is estimated that iNPH may be responsible for nearly 1 to 6% of cognitive issues.

Pathophysiology

Although a common unifying theory to explain the pathogenesis of iNPH is lacking, several putative mechanisms have been suggested (►Fig. 1). Some of these theories include:

1. Poor venous compliance: Abnormal vascular compliance in the superior sagittal sinus of iNPH patients leads to alteration in the absorption of CSF. It also causes attenuation of CSF pulsations that drive CSF flow through the aqueduct.
2. Abnormalities in the regulation of CSF production and absorption, leading to accumulation secondary to impaired CSF flow. These are consequent to altered levels of regulatory molecules, including increased expression of CSF tumor necrosis factor alpha and transforming growth factor beta.

The above processes eventually lead to interstitial edema in periventricular white matter. Interstitial edema, in turn, leads to attenuation of blood flow in crucial prefrontal pathways. This is supported by evidence from nuclear imaging studies. Disturbances in basal ganglia pathways

due to abnormal pulsatile CSF flow play a role in gait and cognitive abnormalities. There is evidence of normalization of low dopamine D2 receptor density after shunt surgery.⁵

Clinical Features

Presence of all three features of the Hakim's triad is representative of severe disease. The presence of all three triad features may not occur in all patients.⁶

Gait Abnormalities

Gait disturbances are typically the most frequently occurring abnormality and initial issue in iNPH.^{6–9} Gait abnormalities have a high propensity to improve after CSF shunt procedure. Patients with iNPH have problems in rising from a chair or a bed. Gait issues have been popularly and evocatively termed as “glue-footed,” “magnetic,” or “apraxic” gait. Typical characteristics include a broad-based and short-stepped hypokinetic gait, reduced foot clearance, outward angulation of toes, and difficulty in turning. Unlike the gait in Parkinson's disease, the arm swing is maintained, and external cueing fails to improve stride length and cadence in patients with iNPH. Features of gait in iNPH are represented in ►Table 1.

Upper limbs may demonstrate the presence of motor issues in the form of bradykinesia, which is usually of mild severity. The development of apparent parkinsonism may be observed in 11%.¹⁰ The presence of strictly unilateral features in iNPH is a red flag for an alternative diagnosis, for example, the presence of concomitant cardiovascular disease.

Urinary Incontinence

Urinary incontinence is present inconsistently and is typically a late symptom. Upper motor neuron type of bladder symptoms, such as frequency and urgency, may be apparent in the initial stages of the disease.¹¹ In advanced stages, double incontinence, that is, both bladder and bowel incontinence, may develop. Urodynamic studies reveal the presence of bladder (detrusor) hyperactivity. The mechanism of urinary dysfunction pertains distension of the periventricular fibers that supply the sacral bladder center, which leads to loss of inhibitory signals by the cortical control centers. Nearly 50% of NPH patients have none to mild urinary complaints, which may be in the form of urgency or frequency only.

Neuropsychiatric and Cognitive Issues

Patients with iNPH may uncommonly present with a pure cognitive syndrome. Exclusive cognitive impairment favors the occurrence of other syndromes, including Alzheimer's disease, which may occur concomitantly with iNPH. Cognitive impairment is mainly due to dysfunction of the subcortical frontal circuitry.^{12,13} Executive function is likely to be usually affected first, leading to poor attention, and psychomotor retardation. Visuospatial dysfunction may also develop. In the late stages, other frontal features may attain prominence, including apathy, amotivation, bradyphrenia, and reduced speech output.

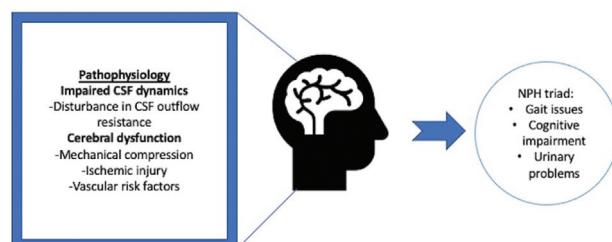


Fig. 1 Pathophysiology of normal pressure hydrocephalus (NPH). CSF, cerebrospinal fluid.

Table 1 Features of gait disturbance in NPH

Feature	Presentation
Cadence	30-foot timed gait test: >13 steps and >10 seconds
Decreased step height	Reduced foot to floor clearance
Wide-based gait	Distance between heels >1 foot length
Short steps	Heel lands less than one foot-length ahead of the toes of the other foot
Tandem gait	> 2-foot corrections/ 8 steps with open eyes
Shoulder-hip counterrotation	Shoulder parallel to hips
Turning	En bloc, 180-degree turn > 3 steps
Posture	Forward leaning
Start hesitation	First step slower/ smaller than subsequent steps
Retropulsion	Positive pull test

Behavioral and psychological issues are also prevalent in iNPH and may often respond to CSF shunting procedures.¹⁴ Overt psychiatric disorders, including major depression, and rarely, mania and psychosis may develop as well.¹⁵ It is important to screen NPH patients for the presence of these psychiatric issues.

Investigations

Neuroimaging

Neuroimaging is essential for diagnosis. Magnetic resonance imaging (MRI) is the preferred imaging modality. MRI enables detailed visualization of various supportive features for NPH. It also supplies vital information pertinent to alternative etiologies, such as vascular changes (→Fig. 2). Radiological features seen in NPH include:

Ventriculomegaly

A. Enlargement of the ventricles, which is out of proportion to parenchymal atrophy, is essential to establish the diagnosis of iNPH. There is symmetrical enlargement of the ventricles. The brunt of ventricular enlargement is borne by the frontal and temporal horns. This may be

accompanied by enlargement of the third ventricle. Corpus callosum may show bowing of the corpus callosum in an upward direction. Periventricular hyperintensity on T2-weighted sequences may also be seen.

B. Callosal index: iNPH is characterized by a narrow callosal angle between the lateral ventricles, which is defined as the angle formed by their roof in anteroposterior projection. An acute callosal angle (less than 90 degrees) favors iNPH.

C. Evans' index (EI): EI is the ratio of the maximal width of the frontal horns of the lateral ventricle, compared with the width of the inner skull in the same plane. EI more than or equal to 0.3 signifies ventriculomegaly.

Changes in Sulcal Size

In iNPH, CSF distribution occurs disproportionately between the subarachnoid space in the caudal and rostral regions. This leads to crowding of gyri in the superior cortical region, and widening of the lateral sulci. Consequently, the lateral sulci appear expanded compared with the cerebral convexity, which is described as "high tight" convexity. This radiological finding is referred to as "disproportionately enlarged subarachnoid space hydrocephalus (DESH)."

CSF Flow Changes

A flow void may be seen on T2-weighted MRI sequences, as a hypointense signal in the cerebral aqueduct. The presence of a flow void sign is linked with augmented CSF aqueductal flow. CSF flow void sign is generally considered a positive prognostic sign indicating probable shunt responsiveness.

Invasive Diagnostic Testing

Spinal Tap Test

CSF tap test/spinal tap test is the most frequently used invasive diagnostic test utilized to forecast response to CSF shunting.¹⁶ Tap test necessitates extraction of 30 to 70 mL CSF via a spinal puncture. CSF opening pressure is recorded. The average opening pressure in iNPH is around 145 mm of water.

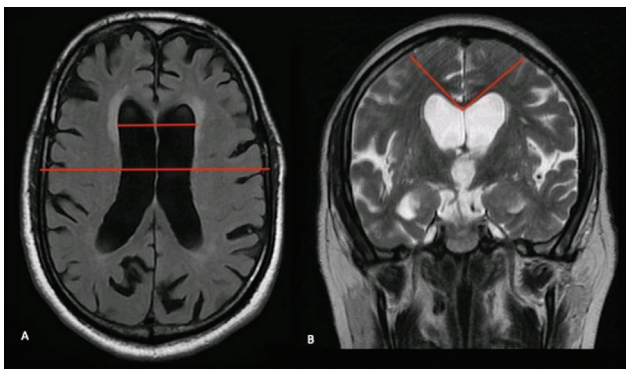


Fig. 2 Magnetic resonance imaging in idiopathic pressure hydrocephalus demonstrating (A) Evans' Index (ratio of widest diameter of frontal horns to widest inner skull diameter; ratio >0.3 consistent with hydrocephalus). (B) Acute angled callosal angle.

Assessment of response includes objective recording of pre-test baseline gait and cognitive dysfunction, which must be performed before the procedure, and 2 to 4 hours after lumbar puncture. Some scales used for evaluation include the iNPH Grading Scale, timed up and go test, short distance straight walking test, and Mini-Mental State Examination.

Improvement may be seen up to 24 hours in gait. If results are equivocal, a repeat lumbar puncture or continuous CSF drainage may be useful. Improvement in gait after lumbar puncture corresponds to a 72 to 100% probability of response to shunt surgery, and is, hence, specific.¹⁷

Extended Lumbar Drainage

An alternative to a high-volume CSF tap is continuous CSF drainage. This is generally at the rate of 5 to 10 mL of CSF/hour for 72 hours. It has the highest predictive value for shunt responsiveness. The positive predictive value is 90 to 100%.¹⁸ In patients with a negative extended lumbar drainage test, risk:benefit ratio must be carefully weighed, in keeping with the patient's considerations.

Concerns with external lumbar drainage include its invasive nature, high cost, and risk of complications, including headache, radiculopathy, and bacterial meningitis.

CSF Hydrodynamic Studies

CSF Infusion Test

This test is used to measure CSF hydrodynamics. The procedure involves subarachnoid instillation of saline or synthetic CSF. Measurements include pressure-volume index, that is, the amount of saline/artificial CSF that raises the CSF pressure by 10 mL of H₂O. Increased pressure-volume index reflects reduced ventricular compliance. Although this test is not commonly performed, it may be useful in diagnosing NPH when the CSF tap test is nonrevealing or noncontributory.

Diagnosis

Diagnostic criteria for iNPH have been elucidated by the Congress of Neurological Surgeons (2005), and the Japanese iNPH guidelines (►Table 2). The important differences between the two guidelines are elucidated in ►Table 3.

Congress of Neurological Surgeons 2005 Guidelines

These were published in 2005 by Marmarou et al.¹⁹ These have three levels of diagnostic certainty for NPH: probable,

Table 2 Guidelines for the diagnosis of idiopathic normal pressure hydrocephalus (iNPH)

Japanese Guidelines, 2021 ¹⁶	Congress of Neurological Surgeons Guidelines, 2005 ¹⁹
<p>Definite iNPH: Definite response to shunt surgery, also referred to as "shunt responder."</p> <p>Probable iNPH: Presence of all the following three features is required:</p> <ol style="list-style-type: none"> 1. Meets criteria for possible iNPH 2. CSF opening pressure of ≤ 200 mm Hg with normal CSF tests 3. One of the following two features on evaluation: <ol style="list-style-type: none"> a. Presence of DESH in combination with gait abnormalities (short steps, shuffling, instability during walking and turning) b. Improvement after CSF tap test or drainage <p>Possible iNPH: Presence of all the following three features:</p> <ol style="list-style-type: none"> 1. At least two symptoms in the clinical triad of gait abnormality, dementia, and urinary urgency 2. No other neurological or nonneurological disease accounting for the symptoms 3. No obvious preceding disease that may account for the hydrocephalus, such as meningitis, subarachnoid hemorrhage, and head trauma 	<p>Probable iNPH: Based on a combination of history, physical findings, neuroimaging, and physiological criteria.**</p> <p>History:</p> <ol style="list-style-type: none"> a. Insidious onset b. Onset > 40 years c. Minimum duration of 3 to 6 months d. No preceding event such as head trauma. e. No other condition explaining the syndrome <p>Brain imaging:</p> <ol style="list-style-type: none"> a. Ventricular enlargement not due to atrophy or congenital hydrocephalus b. No gross CSF outflow obstruction c. At least one of:^a <ol style="list-style-type: none"> i. Temporal horn enlargement ii. Callosal angle ≥ 40 degree iii. Periventricular signal change not due to ischemia or demyelination iv. Aqueductal/ fourth ventricular flow void <p>Clinical: Gait/ balance issues plus at least one other of cognitive/ urinary issues</p> <p>Physiological: CSF opening pressure in the range of 5–18 mm Hg.</p> <p>Possible iNPH: Similar to probable, with a few differences</p> <p>Unlikely iNPH:</p> <ol style="list-style-type: none"> 1. No ventricular enlargement 2. Signs of elevated intracranial pressure 3. None of NPH clinical triad 4. Explained by other conditions

Abbreviations: CSF, cerebrospinal fluid; MRI, magnetic resonance imaging; SPECT, single-photon emission computerized tomography.

^aOther supportive brain imaging findings, which are not required for a "probable" diagnosis: Presymptomatic brain imaging showing small ventricular size/ hydrocephalus, radionuclide cisternogram showing delayed clearance of radiotracer over cerebral convexities after 48 to 72 hours. Cine MRI or other study showing increased ventricular flow rate. A SPECT-acetazolamide challenge showing decreased periventricular perfusion not altered by acetazolamide.

**Refer to Marmarou et al., 2005 for further details.

Table 3 Comparison between Japanese and Congress of Neurological Surgeons Guidelines

Feature	Japanese Guidelines	Congress of Neurological Surgeons Guidelines
Essential symptoms	≥ 1 of the clinical triad	Gait disturbance must be present, with at least one of cognitive or urinary issues
Duration	Not specified	Minimum duration of 3–6 months
Age at onset	After 60 years of age	After 40 years of age
Imaging features	Sylvian fissure and basal cisterns are enlarged DESH	Enlargement of the temporal horns Callosal angle of 40 degree or more Aqueductal or fourth ventricular flow void on MRI Evidence of altered brain water content

Abbreviations: DESH, disproportionately enlarged subarachnoid space hydrocephalus; MRI, magnetic resonance imaging.

possible, and unlikely. The criteria are founded on an amalgamation of clinical history, examination, neuroimaging, and physiological criteria.

Japanese Guidelines on NPH

The Japanese guidelines were first established in 2004. Subsequent revisions were made in 2011 and 2021. These guidelines also provide three degrees of certainty, that is, definite, probable, and possible iNPH.^{16,20}

Differential Diagnosis

Differential diagnosis includes other causes for cognitive impairment. These include Alzheimer's and frontotemporal dementia, which are cortical neurocognitive disorders. Other differential diagnoses may include subcortical syndromes, including dementia with Lewy bodies, Parkinson' disease, corticobasal degeneration, and acquired immunodeficiency syndrome dementia complex. Vascular cognitive impairment and age-related depression (pseudodementia) may also mimic iNPH.

Treatment

Ventricular shunting is the treatment for iNPH. Shunt surgery should be offered to the patient as soon as possible.

CSF Shunt Procedure

Ventriculoperitoneal, ventriculoatrial, or lumboperitoneal shunts may be used. Risk-benefit ratio must first be assessed to determine candidacy for shunting.

Factors Predicting Shunt Responsiveness

Favorable factors include younger age at onset, shorter disease duration (< 1 year), predominant presentation with gait issues, absence of complete triad, and absence of cognitive impairment. Additionally, the presence of minimal cerebral atrophy, secondary hydrocephalus, and early shunt surgery favors good outcomes.

Factors that favor clinical improvement after shunting include clinical improvement after CSF tap test or continuous lumbar CSF drainage, resistance to CSF outflow of more than or equal to 18 mm Hg/mL/min lumbar CSF infusion, and

presence of B waves for more than or equal to 50% during continuous lumbar CSF monitoring.

Features that reduce the odds of positive response to CSF shunting include moderate/severe cognitive impairment, cognitive impairment preceding gait disturbance or present for more than 2 years, aphasia, and MRI features indicating significant white matter changes or diffuse cerebral atrophy.

Shunt Surgery

Based on the type of shunt valve, the shunt may have fixed-pressure valves, which have fixed opening pressure, or a programmable shunt. Programmable shunts have adjustable valve opening pressure, which may be regulated through an extrinsic magnetic program. Shunts may be further categorized as low-pressure, medium-pressure, and high-pressure shunts. Recently, the use of endoscopic third ventriculostomy (ETV) has also been reported. There is limited data on the comparison of the various VP shunts. A meta-analysis comparing these different treatment modalities identified 33 studies. Improvement occurred in more than 75% of patients overall. No significant differences were identified among various treatment methods.²¹

The Japanese Study of iNPH on Neurological Improvement-2 trial was an open-label randomized trial to assess safety and efficacy of lumboperitoneal shunt for iNPH.²² Participants with iNPH were randomized to receive lumboperitoneal shunt surgery within 1 month or after a period of 3 months. Ninety-three patients were randomized. Although a higher number of patients in the immediate surgery arm sustained improvement of one or more points on the modified Rankin scale at 3 months, no difference was apparent between the two groups at 1-year follow-up.

ETV was assessed and compared with VP shunt in a Brazilian randomized trial among 42 patients. ETV led to symptomatic improvement among 50% of the patients at 1 year, compared with 76.9% with VP shunt. Another study comparing ETV and shunting assessed the former to have greater mortality and complications.²³

Clinical Outcome of Shunt Surgery in NPH

In a meta-analysis, 59% patients with NPH demonstrated significant improvement following shunt placement.

However, this improvement persisted in only 29% of patients.²⁴ Some authors have reported a lasting improvement in approximately 75% of patients.

Gait is most likely to improve following the shunt procedure, and cognition is less likely to improve, although patients with significant cognitive impairment have also shown improvement. In a survey of 181 patients diagnosed with NPH, gait was reported to improve in 81.1%, cognition in 64.4%, and bladder symptoms in 55.9%.

Complications

Complications related to shunt surgery include:

- Procedure-related: shunt malposition, anesthesia-related, intracerebral hematoma, subdural effusions, and hematomas
- Shunt-related: valve dysfunction, proximal/ distal catheter obstruction, shunt infections
- Over-drainage headache

The most frequent complication is shunt obstruction. This may manifest as new-onset focal deficits, seizures, and abnormal mentation.

Future Directions

There are several gaps and controversies in diagnostic paradigms and management strategies in iNPH.²⁵ Predictors of shunt response need to be better defined. Even patients who test negative on a CSF tap test may respond to shunting. It is also not clear what the ideal time and how often post-CSF tap test evaluation must be done to document response. The role of biomarkers, particularly in predicting concomitant pathology, must be explored in future studies. There also needs to be agreement on the scales to be used to follow-up with these patients.

Conclusions

NPH is a treatable gait disorder and a reversible type of cognitive impairment. Early diagnosis and management reduced morbidity and disability. Appropriate clinical settings should lead to a thorough workup for this condition, including the eligibility for a shunting procedure. Prognosis worsens the longer NPH remains untreated. Detailed and regular follow-up after shunt surgery is imperative. Future studies must focus on the role of biomarkers, copathology, optimum follow-up parameters, and a unified approach to diagnosis and management worldwide.

Conflict of Interest

None declared.

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