Idiopathic normal pressure hydrocephalus: historical context and a contemporary guide

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ABSTRACT

Idiopathic normal pressure hydrocephalus (NPH) was described in 1965 as a syndrome in which hydrocephalus develops but with a normal cerebrospinal fluid (CSF) pressure, causing shunt-responsive gait apraxia, cognitive impairment and urinary incontinence. Not all patients respond to shunting despite having the clinical syndrome with appropriate radiological features. This has led to considerable debate over subsequent decades regarding idiopathic NPH. It is now understood that asymptomatic communicating hydrocephalus can develop in many healthy older people, and that over time this can develop into a symptomatic state that sometimes responds to CSF shunting, but to a variable extent. This review looks at the historical background of NPH, the use of predictive tests, the current state of clinical evidence for the diagnosis and treatment of idiopathic NPH and the possible underlying causes, to provide a contemporary practical guide for assessing patients with the radiological features of idiopathic NPH.

THE BIRTH OF A CONTENTIOUS SYNDROME

In 1965, Hakim and Adams (Massachusetts General Hospital) described normal pressure hydrocephalus.¹ They reported three patients with cognitive impairment, gait apraxia and urinary incontinence (Hakim’s triad) who each had communicating hydrocephalus on pneumoencephalography and a normal cerebrospinal fluid (CSF) pressure. All three were relatively young (aged 16, 42 and 53 years)¹ and each had a cause for their hydrocephalus: two followed a traumatic brain injury and one had a low-grade lymphocytic process. The patients sometimes declined after pneumoencephalography, an investigation where gas (eg, air or oxygen) was infused into the subarachnoid space using a spinal needle, making the ventricles and subarachnoid spaces visible on skull X-ray.² All three patients dramatically improved after ventriculoatrial shunting.¹ Hakim and Adams hypothesised that an initial increase in CSF pressure led to ventricular enlargement until an equal and opposite pressure was exerted between the ventricles and adjacent brain matter and the CSF pressure relatively normalised (figure 1). A further increase in CSF pressure decompensated this balanced state leading to the Hakim’s triad of symptoms, which could be improved by diverting CSF to an area of lower pressure (CSF shunting).¹

In the same year, Hakim and Adams published another paper describing idiopathic NPH. They reported three slightly older (63, 66 and 62 years old) people with no apparent underlying cause.³ These patients had the Hakim symptom triad but did not always improve after lumbar puncture. They usually declined with pneumoencephalography and all dramatically improved after CSF shunting.³ Importantly, the index case declined after a fall when her ventriculoatrial shunt fractured but then improved after shunt repair, demonstrating an ongoing shunt-dependent condition.³

NOT EVERYONE IS SHUNT RESPONSIVE

Hakim and Adams’ original report of idiopathic NPH was a proof-of-concept paper representing their ‘most striking’ cases. However, when the wider neurological community treated larger numbers, although some responded dramatically to shunting, many showed only modest improvement, and others (up to half in some series) did not respond.³⁻⁴ Those who did respond usually had prominent gait disturbance, with all three symptoms of Hakim’s triad, and clinically they declined after pneumoencephalography, which showed a ‘lack of filling of the subarachnoid spaces over the cerebral convexity’. Invariably those with secondary causes of NPH more frequently responded to shunting.³⁻⁴ However, there were no reliable and specific radiological...
findings that identified people who were ‘shunt responsive’. Isotope brain scanning (scintigraphy) with intrathecal radiolabelled iodine revealed the presence of the tracer in the ventricles in patients with communicating hydrocephalus (but not in controls), and ventricular clearance over time was slow, suggesting obstruction to CSF resorption. While this technique was less hazardous than pneumoencephalography, it still could not predict ‘shunt responsiveness’ reliably.

There were usually high complication rates during investigation and treatment (~30%–40%) with many early series having a significant postoperative mortality of ~7%. Computed tomography (CT) imaging became available in the early 1970s and superseded pneumoencephalography, providing a non-invasive way of showing communicating hydrocephalus (and the cortical atrophy caused by neurodegenerative disease). Intracranial pressure monitoring in patients with idiopathic

Figure 1  Reproduced with permission from Elsevier.
NPH who responded to shunting confirmed Hakim and Adam’s hypothesis that CSF pressure was transiently raised in this condition, with abnormal pressure ‘B’ waves. However, even when using both CT imaging and intracranial pressure monitoring to investigate idiopathic NPH, not all patients responded to therapy.¹⁴

Some authorities suggested that patients with typical clinical and imaging findings who did not respond to shunting must have had the intervention too late to avoid irreversible disease.¹⁴ Others proposed that idiopathic NPH copresents with neurodegenerative disease and those in whom the ‘hydraulic’ component was prominent would respond to shunting, but those with neurodegeneration would not;¹¹ Jacobs noted that some cases had both Parkinson’s disease and idiopathic NPH and postulated that these two disease processes interacted, such that idiopathic NPH ‘precipitated or accelerated’ the parkinsonism; shunting could improve the gait, continence and cognition, but patients still needed levodopa to treat the parkinsonism.⁸

PROVOCATIVE TESTING
Pneumoencephalography was used as both a diagnostic and a provocative test; after it went out of use several groups looked for less invasive provocative tests. Katzman and Hussey described the lumbar infusion study, in which fluid is infused into the lumbar CSF space while the pressure is measured at another lumbar level, thus allowing the measurement of ‘CSF absorption’.¹⁵ ¹⁶ Børgesen and Gjerris used this technique in patients with NPH to measure the compliance of the CSF space and showed that those with increased resistance to a lumbar infusion of Ringer’s solution were usually shunt responsive.¹⁷

Some patients with idiopathic NPH improved after lumbar puncture. Thus, Wikkelso et al. developed the CSF tap test, which involves standardised assessments of gait and cognition before and after a large volume (40 mL) lumbar puncture. They showed that this test could identify a population of shunt-responsive idiopathic NPH cases.¹⁸ However, not all shunt-responsive patients have a positive tap test. This led to the development of the external lumbar drain test, which resembles a CSF tap test except patients had a larger volume of CSF removed via a lumbar drain over a fixed period (usually a few days).¹⁹–²¹

Several well-designed clinical studies have compared these provocative CSF tests. Kahlon et al performed either the lumbar infusion study or the CSF tap test consecutively in 68 suspected NPH cases (primary and secondary) and gave a definitive CSF shunt to anyone positive for either test.²² Overall, 7 were positive for both tests and 81% improved at 6 months: 84% of these had positive lumbar infusion study but only 42% had a positive CSF tap test. Those with a positive CSF tap test were almost always shunt responsive (positive predictive value 94%); the lumbar infusion study had a positive predictive value of 80% but was more sensitive. Unexpectedly, 5 of 21 (24%) non-shunted cases improved at 6 months (2 had prior traumatic brain injury and 1 had aneurysmal subarachnoid haemorrhage) and at follow-up there were no differences between shunted and non-shunted people on gait or cognitive measures. Reassuringly provocative testing caused no complications, but three patients developed a subdural collection and one developed meningitis following ventriculoperitoneal shunting (8.5% complication rate).

Walchenbach undertook a CSF tap test on 49 NPH patients; all non-responders then had an external lumbar drain and all patients (regardless of response) had definitive CSF shunting.²³ This experimental design allowed sensitivity and specificity calculations for each test although there was no non-shunted control group to assess shunt efficacy. As in Kahlon et al.’s study, CSF tap test was not very sensitive (26%) but was highly specific (100%). Meanwhile, an external lumbar drain had benefit similar to a lumbar infusion study, with a sensitivity of 50% and good specificity 80%. Once again, an external lumbar drain was associated with complications, with bacterial meningitis occurring in 4%. Subdural haemorrhage occasionally followed shunt surgery but the authors did not report its frequency.

Meta-analyses have subsequently confirmed that the CSF tap test has a high positive predictive value and that external lumbar drainage also has a high specificity (~85% with wide confidence intervals) but there is no perfect predictive test for shunt responsiveness.²⁴ ²⁵

AN EXISTENTIAL CRISIS
Postmortem findings of patients with shunt-responsive NPH commonly show meningeal fibrosis and deep white matter microvascular changes but with no unique or pathognomonic features.²⁶–²⁸ NPH was an unusual syndrome in which a response to the proposed treatment was also the primary diagnostic criterion. By the early 21st century, there was still no explanation for the lack of a consistent response to CSF shunting. Some meta-analyses of the available evidence showed CSF shunting had a positive effect but systematic reviews of randomised, controlled studies found no evidence to support CSF shunting in NPH.²⁹–³¹ Some clinicians questioned the existence of NPH at all, and the field became radically polarised to ‘believers’ and ‘non-believers’.³²

CLINICAL GUIDELINES
Around 20 years ago, two groups produced clinical guidelines for the diagnosis and classification of idiopathic NPH that are still used today. Ishakawa’s 2004 Japanese Hydrocephalus Society guidelines classified patients as having ‘possible idiopathic NPH’ if they were >60 years of age with imaging features of hydrocephalus and at least two of Hakim’s symptom triad, and with no alternative explanation for their symptoms.³³ Patients with a normal lumbar puncture opening pressure and a response either to CSF tap test, external lumbar drain or lumbar infusion study, are classified as ‘probable idiopathic NPH’.
Those who respond to surgery are classified as ‘definite idiopathic NPH’. Relkin et al. published joint American, German and Swedish guidelines in 2005 and defined ‘probable’ idiopathic NPH strictly as occurring in people aged over 40 years who have all three of Hakim’s triad with hydrocephalus on imaging and a normal CSF opening pressure. The Relkin criteria for ‘possible idiopathic NPH’ are more permissive, including patients with isolated gait disorder or cognitive decline if they have imaging findings of ventriculomegaly. Relkin et al were
A pragmatic approach to investigating idiopathic Normal Pressure Hydrocephalus (iNPH)

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<th>Brain Imaging</th>
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<td>• Evan’s Index &gt;0.3</td>
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<td>• INPH RADSCLAE &gt;4</td>
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<td>• No secondary causes of hydrocephalus</td>
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YES → Unlikely iNPH

NO → Clinical symptoms

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<th>Clinical symptoms*</th>
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YES → Asymptomatic hydrocephalus

NO → 40ml CSF tap test shows

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<th>40ml CSF tap test shows</th>
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<td>• normal opening pressure and CSF contents**</td>
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<td>• improvement in timed walk by &gt;10%</td>
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YES → Refer for shunt surgery

NO → 48 hour Lumbar drain or Lumbar infusion test

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<td>Improvement in timed walk by &gt;10% or NCsf of &gt;1.3 mmHg/ml/min</td>
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YES → Refer for shunt surgery

NO → Shunt non-responsive iNPH or alternate diagnosis

Figure 3 The investigation and management pathway of idiopathic NPH at Imperial College London Healthcare NHS Trust. **Not explained by another neurological condition, for example, PSP. ** Patients with abnormal CSF contents and/ or raised CSF neurofilament light should be further evaluated before further NPH provocative testing. CSF, cerebrospinal fluid; iNPH, idiopathic normal pressure hydrocephalus; PSP, progressive supranuclear palsy.

‘NO PLACEBOS, PLEASE’: CLINICAL TRIAL EVIDENCE

Patients with idiopathic NPH may be reluctant to enrol into clinical trials in which they might not receive shunt therapy. In 2011, Tisell et al sidestepped this problem by using a ‘one-arm crossover’ trial design in which all patients received CSF shunts but only half had these activated on insertion; all patients had an operation (or sham) halfway through the study and those whose shunts had initially been tied closed had them opened, so all patients ended the trial with active shunts. The trial was double blinded and neither assessors nor patients knew their shunt activation status until the final intervention. Although this trial was a small study of a specific population who had severe vascular disease and idiopathic NPH unresponsive to a CSF tap test, the design is now the gold-standard in clinical trials for this condition. In 2015, Kazui et al used a similar design in SINPHONI-2, a prospective, randomised control trial of immediate vs delayed lumboperitoneal shunt in probable idiopathic NPH. They found that lumboperitoneal shunts modestly reduced disability, cognitive and gait impairment. Toma and Watkins performed a prospective randomised, double-blind one-arm cross-over trial with programmable ventriculoperitoneal shunts in probable idiopathic NPH. This trial was ended due to incomplete enrolment; the full dataset has not been published but a brief report on a sample size of only 14 patients showed an improved primary outcome (gait speed) at 3 months after the shunt. Two further prospective, double-blinded randomised controlled trials in the USA using ventriculoperitoneal shunts and a ‘one-arm crossover’ trial design, the ARCS-NPH and the PENS feasibility study, have completed but the results are not yet published. A larger scale version of PENS is due to recruit in the USA.
in 2022. A Cochrane systematic review is currently evaluating the pooled analysis of these studies. A limitation of the ‘one-arm crossover’ trial design is that it sacrifices outcome data from the long-term control arm. Large-scale prospective follow-up data for shunted patients suggest that the benefit of ventriculoperitoneal shunting persists for years before decline. While complication rates remain relatively high at 20–30%, most are now managed non-surgically.

WHAT CAUSES IDIOPATHIC NPH?
There have been several plausible disease mechanisms proposed for NPH, including direct cortical mass effect, reduced CSF absorption, reduce periventricular blood flow and reduced lymphatic clearance. However, the underlying cause of the hydrocephalus remains uncertain, although genetic cases may hold a clue. Several family pedigrees have been described with inherited idiopathic NPH. In 2019, Morimoto et al identified a CFAP43 mutation in a Japanese kindred with autosomal dominant hydrocephalus. Subsequently, Yang et al have identified CWH34 mutations in 15% of a non-familial idiopathic NPH cohort. CWH43 is a glycosylphosphatidylinositol anchor protein expressed in the ventricular epithelia, and CWH43 mutation knock-in mice have reduced ventricular cilial density and function, providing further evidence that cilial function may be linked to the development of hydrocephalus. SFMBT1 is a protein of uncertain function that is expressed in the choroid; patients with idiopathic NPH (several cohorts) have a higher rate (10–26%) of heterozygous copy number loss in SFMBT1 than age matched controls (4–5%). Although multiple genetic factors influence the development of hydrocephalus, there are also environmental associations. For example, prospective studies have shown that 90% of people with idiopathic NPH have obstructive sleep apnoea, and the prevalence of idiopathic NPH is much higher in people with schizophrenia and diabetes than in age-matched controls.

**Idiopathic NPH and the role of ageing and neurodegenerative disease**
Prospective screening population studies suggest that up to 6% of people aged over 65 years fulfil clinical and radiological criteria for possible idiopathic NPH, and that this percentage increases with age. There are also reports of asymptomatic patients with radiological features of idiopathic NPH. With long-term follow-up, many become symptomatic, consistent with Hakim and Adams’ original hypothesis that hydrocephalus develops asymptotically before causing clinical symptoms. Some people with asymptomatic hydrocephalus probably develop Hakim’s triad from underlying neurodegenerative disease that is not shunt-responsive. In particular, patients with progressive supranuclear palsy develop imaging features of hydrocephalus more than those with Parkinson’s disease, Alzheimer’s dementia or normal controls. The few available postmortem studies in idiopathic NPH show that many cases have Alzheimer’s dementia or vascular pathology at time of death but progressive supranuclear palsy pathology occurs more frequently than expected. Frontal or parietal cortical biopsies taken at the time of ventriculoperitoneal shunt insertion or intracranial pressure monitoring show that Alzheimer’s dementia develops in 30%–60% of cases; there are contrasting reports about whether this influences the effect of CSF shunting. Recent studies suggest that patients with low CSF neurofilament light, total tau, abeta 1–40 and pTau181 are more likely to respond to shunting. It may be that people with higher markers of neurodegeneration...
have asymptomatic hydrocephalus and an underlying neurodegenerative disease.

### A pragmatic approach to assessing idiopathic NPH

Large case series have shown that many patients presenting with idiopathic NPH have an alternative cause for their symptoms. In a large prospective US idiopathic NPH register, 26% of cases did not undergo provocative testing and 46% of patients had shunted surgery. This, therefore, a careful neurological history and examination is required to exclude NPH mimics and alternative explanation for patient symptoms.

At the NPH clinic in Imperial College Hospital, London, we accept the limitations of the current evidence and follow the Japanese Hydrocephalus Society and Relkin guidance, broadly incorporating idiopathic NPH Radscale imaging scores. Multidisciplinary working with neurologists, neuroradiologists, neurotherapists and neurosurgeons is key. It is important to note that the investigation and treatment of idiopathic NPH is highly invasive. We are explicit about this in initial discussions with the patient and family so they can make an informed decision about proceeding. Equally it may not be appropriate to perform invasive testing or shunt surgery on frail patients with multiple co-morbidities and this must be considered at the early stages of the assessment. We do not usually consider a diagnosis of idiopathic NPH if the idiopathic NPH Radscale Score is <4 (figure 3). Patients with imaging features of idiopathic NPH referred to our neurology-led clinic are assessed clinically and with subsequent discussion of their imaging in a specialist dementia neuroradiology multidisciplinary team meeting. Patients may then have dopamine transporter (DaT), single-photon emission CT (SPECT), amyloid positron-emission tomography (PET) and fluorodeoxyglucose (FDG)-PET imaging as indicated on a case-by-case basis. We do not investigate asymptomatic patients further but counsel them to return if they develop Hakim’s triad symptoms (figure 4). If patients have a higher-order gait dysfunction with no other identified cause then they have a 40 mL CSF tap test with a therapist-led 10m timed walk. The timed walk is performed in triplicate immediately before and at a minimum of 4 hours after the CSF tap test. Our experience suggests that some people’s triplicate values vary with fatigue effects, and so we compare the lowest values acquired. Out of interest, we screen cognition before and after the CSF tap test but do not require cognitive improvement to define shunt responsiveness, as cognition can take many months to improve following definitive ventriculoperitoneal shunt surgery. It is important to note that the original 1982 Wikkelsø CSF tap test protocol showed that gait speed can improve up to a week following the test, but in our practice it is not possible to repeat carefully observed gait assessments over this period, so we instead consider subjective reports of improvements in the week following the CSF tap test. At the time of CSF tap test we also carry out neurodegenerative biomarker assessment including CSF neurofilament.
Further reading


Key points

► Idiopathic normal pressure hydrocephalus (NPH) should be considered in patients who have dominant gait dysfunction with cognitive and urinary symptoms; there is some high-quality evidence to justify cerebrospinal fluid shunting in such cases.
► Ventriculomegaly is a common and non-specific finding in elderly people but NPH has some specific radiological features.
► The radiological features of NPH initially develop asymptomatically, so it is important to exclude alternative causes in patients whose symptoms suggest idiopathic NPH.

CONCLUSIONS

Neurologists commonly encounter people with the syndrome of idiopathic NPH, which has specific radiological features and can be CSF shunt responsive. It is essential that such patients are assessed by clinicians with the experience to identify and manage NPH mimics and to perform standardised provocative tests to help to determine who will benefit from CSF shunting. There is little high-quality evidence on which to base practice and we need further work—including more randomised controlled trial evidence on the use of CSF shunting—to understand the cause and to characterise the radiological features associated with shunt-responsive idiopathic NPH. Going forward, we need to characterise patients with possible idiopathic NPH not just by the presence of vascular disease and amyloid status but also by synuclein, tau as well as non-specific markers of neuronal loss such as neurofilament light to understand the interaction between neurodegenerative disease and idiopathic NPH. Such an approach will need to be large scale, co-ordinated and collaborative. This approach will also open the door to potential disease-modifying trials in patients with shunt-unresponsive hydrocephalus who traditionally have been clinically neglected.

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