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Dementia (J Pillai, Section Editor)

Current Update on Treatment Strategies for Idiopathic Normal Pressure Hydrocephalus

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Abstract

Purpose of review Idiopathic normal pressure hydrocephalus (iNPH) is a surgically treatable neurological disorder of the elderly population that is characterized by abnormal ventricular enlargement due to cerebrospinal fluid (CSF) accumulation and gait disturbance, cognitive impairment, or urinary incontinence. The objective of this review is to present the current diagnostic and treatment approaches for iNPH and to discuss some of the postoperative modalities that complement positive surgical outcomes.

Recent findings Although historically reported patient outcomes following iNPH surgery were dismal and highly variable, recent advances in terms of better understanding of the iNPH disease process, better standardization of iNPH diagnostic and treatment processes arising from the adoption of clinical guidelines for diagnosis, treatment and in research methodologies, and availability of long-term follow-up data, have helped reduce the variations to a much improved 73 to 96% reported good outcomes.

Summary With careful evaluation, good patient selection, and advanced surgical techniques, iNPH can be surgically treated to return patients close to their pre-iNPH functional status. Institution of an interdisciplinary effort to rehabilitate patients following surgery may help augment their recovery.

Introduction

Hydrocephalus is a debilitating neurological disorder that may be operationally defined as the pathological accumulation of cerebrospinal fluid (CSF) within the cerebral ventricles due to obstruction of CSF circulation, or a mismatch between normal CSF production and low resorption into the systemic circulation [1]. In many forms of hydrocephalus, the ventricular enlargement is associated with raised intracranial pressure (ICP) [2, 3]. However, in the early 1960s, Dr. Salomon Hakim described a group of patients who had developed hydrocephalus, yet had unexpectedly low-normal ICP, which he termed normal pressure hydrocephalus (NPH) [4, 5]. While Dr. Hakim's initial NPH patients had sustained neurological injury, such as hemorrhage or trauma, prior to their hydrocephalus diagnosis, subsequent reports described elderly NPH patients who had no identifiable risk factors [6]. Thus, NPH was historically classified into secondary (sNPH) and idiopathic (iNPH), to differentiate those who have known causes from those who do not have any known risk factors for hydrocephalus [7]. We recommend abandoning the use of sNPH to describe acquired or unrecognized congenital adult hydrocephalus [8]. While these patients may have some symptoms that are similar to those with iNPH, the other clinical characteristics, pathophysiology, diagnostic strategy, and treatment response are significantly different when compared to those of patients with actual iNPH.

To clinically diagnose iNPH, the patient must be elderly (≥age 60 years), have abnormal ventricular enlargement demonstrated on cranial computed tomography (CT) or magnetic resonance imaging (MRI), and must have at least one of the iNPH triad of neurologic symptoms: gait disturbance, cognitive impairment, and urinary incontinence [9, 10]. Many experts consider gait impairment an essential symptom (Table 1).

iNPH is the most common form of hydrocephalus in the elderly, with reports of prevalence ranging from 10/100,000 to 5900/100,000 [11, 12] with a mean of 175/100,000 [13•]. In addition, the reported epidemiology is heterogeneous and varies from region to region [13•].

While the pathophysiology of iNPH development and recovery of neurologic impairment has not been fully characterized [14], there is evidence that the combined effects of impaired CSF flow dynamics, perturbed CSF biochemistry, and cerebrovascular compromise are mechanisms that mediate secondary brain injury mechanisms such as neuroinflammation, oxidative damage, and hypoxic-ischemic injury [15–19].

Over the past few decades, significant strides have been made in terms of iNPH diagnosis and care. However, the only effective treatment for iNPH is surgical CSF shunting. The primary goal of CSF shunting in iNPH is to compensate for the impaired CSF resorption by draining a sufficient amount of CSF to abrogate the cascades of secondary brain injury. However, the exact mechanisms of restoration of neurologic function in iNPH are not fully understood [20, 21]. Several pharmacological treatments for iNPH have been investigated [22], but to date there are no non-surgical therapies for the effective treatment of iNPH.

Following iNPH surgery, functional improvement strategies such as physical, occupational, and speech therapies, as well as social support, are often needed to return patients to their pre-iNPH functional status.

Table 1. Differential diagnosis of suspected iNPH ([6])

	Gait	Dementia	Incontinence
Disorders that may have all 3 symptoms			
iNPH, with or without comorbidities	X	X	X
Parkinsonism	X	X	X
Lewy body dementia	X	X	X
Corticobasal degeneration	X	X	X
Progressive supranuclear palsy	X	X	X
Multiple system atrophy	X	X	X
Vascular dementia	X	X	X
Neurosyphilis	X	X	X
Medication side effects	X	X	X
Multifactorial—any combination of diagnoses, with or without iNPH	X	X	X
Disorders that may have 2 symptoms			
Multifactorial—any combination of diagnoses, with or without iNPH	X	X	X
iNPH, with or without comorbidities	X	X	X
Vitamin B12 deficiency	X	X	
Cervical stenosis and myelopathy	X		X
Lumbosacral stenosis	X		X
Peripheral neuropathy	X		X
Disorders that may have only one symptom			
iNPH	X		
Degenerative arthritis of the hips, knees, ankles	X		
Spinocerebellar degeneration	X		
Peripheral vascular disease (claudication)	X		
Alzheimer dementia		X	
Frontotemporal dementia		X	
Depression		X	
Hypothyroidism		X	
Sleep apnea		X	
Prostatic hypertrophy/obstructive uropathy			X
Pelvic floor abnormalities			X
Interstitial cystitis			X
Disorders that can aggravate other symptoms			
Visual impairment	X	X	
Hearing impairment		X	
Obesity	X		
Cardiovascular disease	X		
Pulmonary disease	X		
Chronic lower-back pain	X		
Vestibular disorders	X		

Reproduced with permission from Williams and Relkin ([6])

The objective of this review is to present the current diagnostic and treatment approaches for iNPH and to discuss some of the postoperative modalities that complement positive surgical outcomes.

Diagnostic evaluation

Initial assessment

The clinical approach to iNPH includes thorough history taking, physical examination, and careful review of imaging not only to diagnose the condition, but to rule out other differential diagnoses that could be responsible for the patient's signs and symptoms. The examination also serves to record the patient's pretreatment functional status as a benchmark for postoperative follow-up if the patient has shunt surgery.

The syndrome of iNPH is often conceptualized as dementia, gait impairment, and incontinence, but because these symptoms have so many different causes in the elderly, it may be better thought of as frontal/subcortical cognitive impairment, neurologic gait impairment, and neurologic bladder impairment. These distinctions are crucial, as patients whose symptoms are from comorbidities rather than iNPH do not benefit from shunt surgery [23].

Gait assessment

Approximately 94–100% of iNPH patients initially present with signs and symptoms of gait disturbance [10, 24]. Although the pattern and severity of gait impairment varies from one patient to another, the typical iNPH gait includes retropulsion or anteropulsion of stance, hesitation or failure to initiate gait, slow, shuffling and wide-based gait, reduced foot clearance, and difficulty with turning. These features are considered typical of a higher-level gait disorder, which is characterized by difficulty integrating sensory information about the position of the body in its environment, including the effect of gravity, which results in disturbed or absent postural and locomotor reflexes *in the absence of primary sensorimotor deficits* [25, 26]. There are several tests available that may be used to assess gait, such as the timed up-and-go test, Tinetti assessment tool, 10-m walk test, and the Boon scale [27–30]. Care must be taken to exclude other causes of gait impairment, such as sensory ataxia, cervical myelopathy with spastic gait features, or lumbar spinal stenosis with neurogenic claudication, as well as non-neurologic causes, including osteoarthritis, deconditioning, frailty, or medication side effects. Gait impairment is frequently considered an essential symptom of iNPH, and if the gait is normal, then a search for other causes of the patient's syndrome is indicated before performing tests that are specific for iNPH.

Cognitive assessment

Cognitive impairment is identified in approximately 78–98% of iNPH patients [6, 10, 31]. However, the number of affected cognitive domains including attention, concentration, executive function, working memory, recall memory, visuo-constructional skills, and conceptual thinking varies

between patients [32, 33]. Apathy, amotivation, and hypersomnolence are often present. The severity of cognitive impairment is also variable and may range from mild cognitive impairment to dementia [6]. Cognitive screening may be performed by established tests, such as the Montreal Cognitive Assessment [34]. The differential diagnosis includes, but is not restricted to, vascular dementia, Lewy body dementia, frontotemporal dementia, Parkinsonism with dementia, and medication side effects. Not typical for iNPH are impaired language and naming, rapid forgetting not helped by cues (amnestic pattern), loss of autobiographical memory, hallucinations, or delirium [6]. Formal neuropsychological evaluation can be helpful in identifying the pattern of cognitive impairment. Depression is a common comorbidity in patients with iNPH [35], and screening and appropriate concurrent treatment should be considered. Because delirium can have significant negative impact on cognitive performance and is not a feature of iNPH, patients with delirium should not be assessed for iNPH until the delirium has been completely resolved, which typically means waiting to see them in the outpatient setting [6].

Urinary incontinence evaluation

At initial presentation, approximately 76–83% of iNPH patients have symptoms of urinary incontinence, frequency, and urgency. Diligent characterization of a patient's urinary dysfunction is imperative to rule out other neurogenic or urologic causes of incontinence that may mimic iNPH, including myelopathy, overactive bladder syndrome, prostate disease, and pelvic floor dysfunction [6, 10, 36]. Mixed disorders may be present, or iNPH urinary incontinence may represent a change from a prior pattern of incontinence.

Radiological evaluation

Radiologic assessment requires a careful review of imaging to establish the patient has abnormally enlarged ventricles, rule out any potential confounding etiologies such as obstructive hydrocephalus, and set a baseline for follow-up imaging [23]. There are several approaches for objectively assessing ventricular size [37, 38], but the most commonly used is the Evans index. The Evans index is obtained as the ratio of width of frontal horns divided by the widest cranial diameter measured from the inner table of the skull on the same slice [39] (Fig. 1). Evans index >0.3 is considered abnormal, but it is not specific for iNPH and should be interpreted within the clinical context because approximately 21% of patients over the age of 70 have an Evans index greater than 0.3 [39]. Another radiologic measure that is gaining use is disproportionately enlarged subarachnoid space hydrocephalus (DESH). DESH is a specific pattern of hydrocephalus that is characterized by 3 features, including ventriculomegaly as described above, the so-called high-tight convexity with effacement of the subarachnoid space at the vertex, and enlargement of the Sylvian fissures [40] (Fig. 2). Although DESH has shown promise for predicting shunt responsiveness [40–42], it is not a requirement for iNPH diagnosis [43].

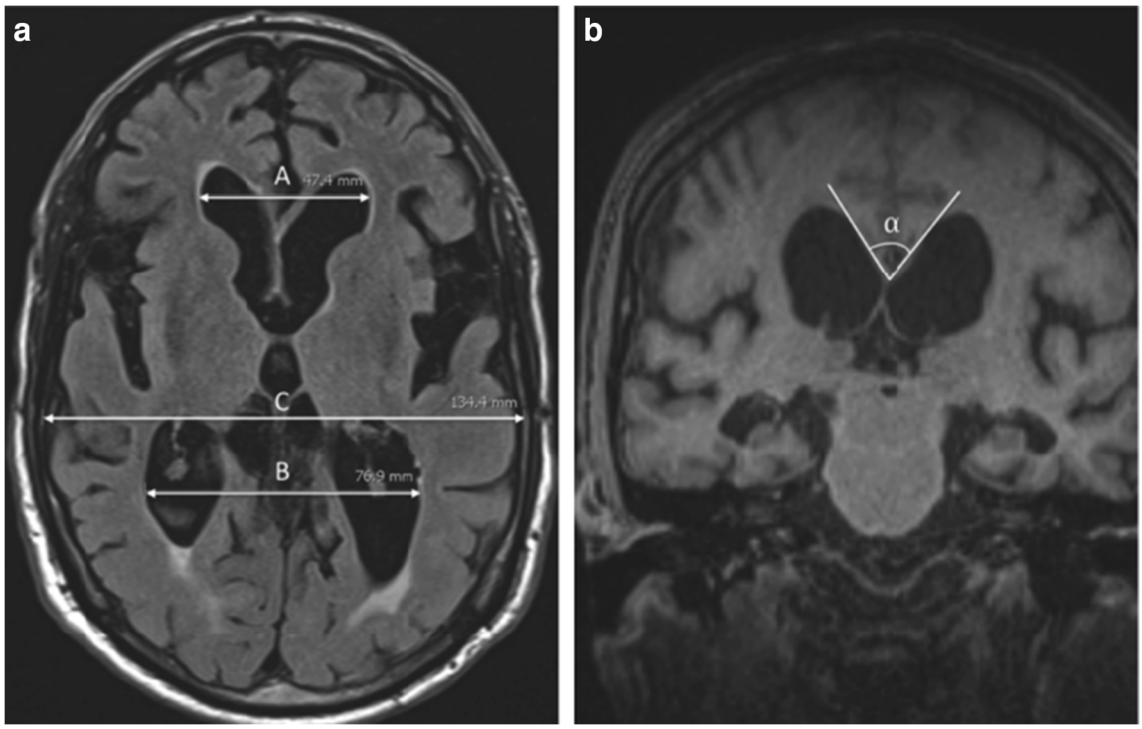

Fig. 1. MRI images of an 83-year-old male with iNPH. **a** An axial T2-FLAIR image demonstrating enlarged ventricles with Evan's ratio (A/C) of 0.35 and a frontal and occipital horn ratio (A+B)/2C of 0.46. **b** A coronal T1-weighted image demonstrating a callosal angle, *α*, of 70% at the level of the posterior commissure. Reproduced from Isaacs et al. [52] with permission).

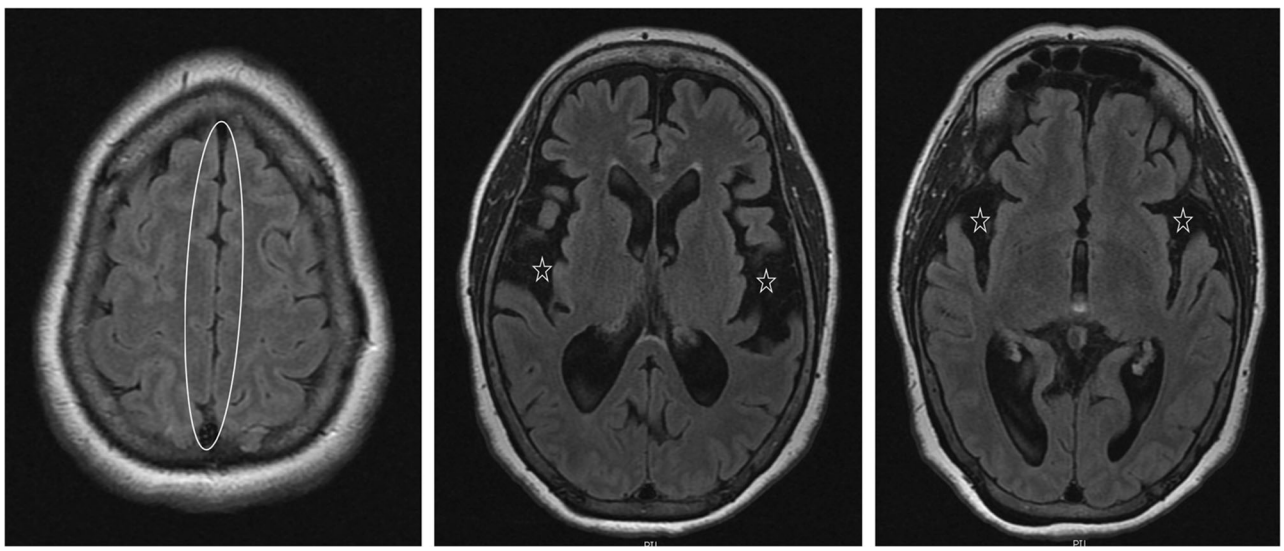

Fig. 2. Axial T2 FLAIR MRI images of an iNPH patient demonstrating minimal sulcal spaces at the vertex (circled) despite disproportionately enlarged subarachnoid spaces in the lower sequences (star) consistent with a DESH pattern of hydrocephalus. Reproduced from Williams and Relkin [6] with permission.

Table 2. Comparison between the International and Japanese guidelines for the diagnosis of iNPH ([6])

Feature	International guidelines	Japanese guidelines
Essential symptoms	Findings of gait/balance disturbance must be present, plus at least one other area of impairment in cognition, urinary symptoms, or both	More than one of the clinical triad: gait disturbance, cognitive impairment, and urinary incontinence Gait disturbance is the most prevalent feature, followed by cognitive impairment and urinary incontinence
Symptom onset	Insidious	Symptoms progress slowly
Symptom duration	Minimum duration of 3–6 months	
Age at onset	After age 40 years	After age 60 years
Etiology	No evidence of an antecedent event such as head trauma, intracerebral hemorrhage, meningitis, or other known causes of secondary hydrocephalus	Preceding diseases possibly causing ventricular dilation are not obvious, including subarachnoid hemorrhage, meningitis, head injury, congenital hydrocephalus, and aqueductal stenosis
Comorbid disorders	No other neurologic, psychiatric, or general medical conditions that are sufficient to explain the presenting symptoms	Clinical symptoms cannot be completely explained by other neurologic or non-neurologic diseases Other neurologic diseases, including Parkinson disease, Alzheimer disease, and cerebrovascular diseases, may coexist but should be mild
Gait impairment	At least 2 of the following should be present and not be entirely attributable to other conditions • Decreased step height • Decreased step length • Decreased cadence (speed of walking) • Increased trunk sway during walking • Widened standing base • Toes turned outward on walking • Retropulsion (spontaneous or provoked) • En bloc turning (3 or more steps for 180°) • Impaired walking balance, as evidenced by 2 or more corrections out of 8 steps on tandem gait testing	Small stride, shuffle, instability during walking, and increase of instability on turning
Urinary urgency/incontinence	One of the following should be present: • Episodic or persistent urinary incontinence not attributable to primary urologic disorders • Urinary and fecal incontinence • Or any 2 of the following should be present: • Urinary urgency (frequent perception of a pressing need to void) • Urinary frequency (more than 6 voiding episodes in an average 12-h period) • Nocturia (the need to urinate more than twice a night)	Overactive bladder, mainly manifesting as increased nocturnal urinary frequency, urgency, and urinary incontinence
Cognitive impairment	Documented impairment (adjusted for age and educational attainment) or decrease in performance on a cognitive screening instrument, or both Or evidence of at least 2 of the following on examination that is not fully attributable to other conditions: • Psychomotor slowing (increased response latency) • Decreased fine motor speed • Decreased fine motor accuracy • Difficulty dividing or maintaining attention	Cognitive impairment is detected on cognitive tests

Table 2. (Continued)

Feature	International guidelines	Japanese guidelines
	• Impaired recall, especially for recent events • Executive dysfunction • Behavioral or personality changes	
Ventricular size	Ventricular enlargement not entirely attributable to cerebral size atrophy or congenital enlargement (Evans index .0.3 or comparable measure)	Ventricular dilation (Evans index .0.3)
Other neuroimaging features	No macroscopic obstruction to CSF flow	Sylvian fissures and basal cistern are usually enlarged
	At least one of the following supportive features: • Enlargement of the temporal horns of the lateral ventricles not entirely attributable to hippocampus atrophy • Callosal angle of 40° or more • Evidence of altered brain water content, including periventricular signal changes on CT and MRI not attributable to microvascular ischemic changes or demyelination • An aqueductal or fourth ventricular flow void on MRI	Periventricular changes are not essential Narrowing of the sulci and subarachnoid spaces over the high convexity/midline surface (DESH)
CSF pressure	CSF opening pressure in the range of 5–18 mmHg (or 70–245 mmH_2O), as determined by LP or a comparable procedure; appropriately measured pressures that are significantly higher or lower than this range are not consistent with a probable NPH diagnosis	CSF pressure of #200 mmH_2O and normal CSF content

Abbreviations: *DESH* disproportionately enlarged subarachnoid space hydrocephalus, *LP* lumbar puncture
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Care should be taken to exclude the possibility of obstructive hydrocephalus resulting from aqueductal stenosis, brain tumor, or fourth ventricle outlet obstruction, as these forms of hydrocephalus may be seen in the elderly. If found, CSF removal via lumbar puncture may be contraindicated, and the decision to treat should follow the standards for obstructive hydrocephalus.

Differential diagnosis and comorbidities

Because iNPH occurs in the elderly population that tends to have multiple health conditions and comorbidities, such as osteoarthritis, cardiovascular disease, cerebrovascular disease, Alzheimer dementia, diabetes, depression, medication side effects, and vision impairment [20, 35, 44–50], the need to rule out other diagnoses, and treat them if found, cannot be overemphasized (Table 2). A list of differential diagnoses of iNPH has been previously reviewed [6, 51, 52].

Another important issue to consider when assessing iNPH patients is that a significant proportion of the patient population are on antithrombotic medications for indications such as primary prevention of cardiovascular diseases, atrial fibrillation, vascular stents, or

venous thrombosis, which places them at risk for perioperative bleeding [53–55]. Assessment of the risks and benefit of withholding antithrombotic agents for iNPH diagnostic tests and treatment should be carefully assessed on a case-by-case basis, as the need for anticoagulation is not necessarily a contraindication to the evaluation and treatment of iNPH [55, 56]. The timing and duration for holding medications prior to iNPH surgery have been previously reviewed [55, 57].

Diagnostic criteria

Presently, two major published clinical guidelines for the diagnosis and treatment of iNPH exist: the international [9, 24] and the Japanese guidelines [10, 58, 59] (Table 1). The American Academy of Neurology has also presented recommendations that complement the two major guidelines [60]. Although nuances between the guidelines exist, consensus exists that iNPH diagnosis requires the following: the patient should be age 60 years or older; radiographic evidence of abnormal ventricular enlargement with an Evans ratio >0.3 should be present; and the patient should have at least one of the primary symptoms (gait disturbance, cognitive impairment, or urinary incontinence). While the level of evidence reviewed to arrive at the conclusions and recommendations in the guidelines was variable and ranged from Sackett Grades I to V [61], the guidelines were developed by expert consortiums who reviewed the best available data. and updates to the guidelines have been provided when necessary [10, 59, 62].

Pre-surgical confirmatory tests

If iNPH remains a possibility after exclusion or treatment of comorbid disorders, then testing to predict whether surgery is likely to benefit the patient is usually performed [9, 24]. There are three main tests, including the tap test (also known as large volume lumbar puncture), drainage of CSF via a spinal catheter, known as external lumbar drainage (ELD), and infusion testing. The physiologic premise of the tap test and ELD is that the patient's response to short-term drainage of CSF should predict the response to long-term drainage of CSF after shunt surgery. Before the CSF removal, formal evaluation of gait should be performed. Formal evaluation is required, as reliance solely on the report of the patient and family may be biased by the hope to see a response. Some centers also assess cognition. Following CSF removal, these tests are repeated, and the results are compared to the baseline results to assess for clinical improvement. Demonstration of improvement has been shown to be predictive of a favorable response to shunt surgery [6, 63, 64]. Nevertheless, lack of improvement following a confirmatory test should be evaluated on a patient-by-patient basis to determine need for further testing or bypass to shunt surgery, as the predictive values of the confirmatory tests are not perfect.

Tap test

Standard procedure

The tap test involves performing a standard lumbar puncture to remove a large volume of CSF from the lumbar CSF space. The patient may be positioned in the lateral decubitus or seated position. After prepping with topical antiseptic and applying sterile drapes, local anesthesia is infiltrated midline in the back at the L3–4 or L4–5 interspace. An LP needle is then inserted and advanced until CSF is encountered. Approximately 30–50 mL of CSF is collected, and the LP needle is removed. Measurement of opening pressure is not necessary, as the information does not confirm or refute the diagnosis of iNPH.

Contraindications

Lumbar puncture is contraindicated in the presence of obstructive hydrocephalus and should not be performed on patients receiving anticoagulation or anti-platelet therapy until the effect of these agents has been corrected. The LP needle should not be inserted through infected skin or tissue, as may be seen with pressure ulcers.

Complications

The most common complication associated with performing an LP is the post-LP headache, which occurs in 10–30% of all patients [65, 66]. However, experts have noted that the rate of post-LP headache is significantly lower in the elderly population being evaluated for iNPH. In the general population, bed rest has not been shown to significantly decrease the risk of post-LP headache [65, 66], and because the purpose of the tap test is to assess gait and mobility, many centers have patients upright immediately after the LP is completed and have them lie down only if they develop significant low-pressure symptoms.

Special points

As described above, gait and cognition must be evaluated before the LP is performed. Typically, patients are upright for 3 to 4 h after the LP before retesting gait and cognition. However, there is variability in the timelines of patient response following the tap test [67]. Therefore, it is recommended that patients who do not show improvement at 4 h post-LP may be retested at approximately 6 h. The positive predictive value (PPV), negative predictive value (NPV), and accuracy of the tap test for a favorable response to shunting are approximately 73–100%, 16–42%, and 45–54% respectively [68, 69].

Cost/cost-effectiveness

The tap test is the least expensive of the three iNPH tests, as it can be done in the outpatient setting and does not require any special equipment or

prolonged monitoring. Costs are increased at centers that have LPs performed under fluoroscopic guidance and have physical therapy evaluate the gait before and afterwards [70].

External lumbar drainage

Standard procedure

The objective of external lumbar drainage (ELD) is similar to the tap test, i.e., to remove a large volume of CSF and assess the patient's response. The main difference, however, is that ELD involves continuous CSF removal at a relatively low rate (10 mL/h) for 2 to 3 days. The total volume of CSF removed is higher, however, at a slower rate. Additionally, the duration of the CSF drainage effect is longer. Because a catheter must be passed through the needle for insertion, a larger diameter needle for the lumbar puncture (16- or 17-gauge Touhy) is required; however, in most circumstances, a longer needle is not needed. Once the lumbar catheter is in place and secured, it is connected to an external drainage system that is leveled to the external acoustic meatus for continuous CSF drainage, similar to the approach used for CSF drainage via an intraventricular catheter. At the end of the CSF drainage trial, the catheter is removed, and gait and cognitive reassessments are performed.

Contraindications

Similar to the tap test, contraindications include obstructive hydrocephalus, coagulopathy, and infection at the planned insertion site. Additionally, in the presence of significant scoliosis, lumbar spinal stenosis, or existing spinal instrumentation, fluoroscopic guidance for the LP and catheter insertion is recommended.

Complications

The most significant risk with ELD is infection, which occurs in 2–3% of patients [71]. Single-dose antibiotic prophylaxis is recommended so that the dose is fully administered 0–60 min prior to insertion of the needle. Low-pressure headache may occur with continuous CSF drainage; however, the drainage can be stopped or slowed in response. Catheter fracture is uncommon but may be a slightly higher risk in patients with significant spinal stenosis. Fracture of the catheter has also been reported at the time of removal.

Special points

As with the tap test, evaluation of gait and cognition must be performed prior to insertion of the spinal catheter, and upon completion of the CSF drainage. The ELD protocol is complex and should be done only at centers where a formal protocol is used and the expertise to perform and interpret the tests results is present. The ELD may be done as the first-line test or in patients who have not demonstrated improvement with the tap test. There

is evidence that the ELD is a more reliable method for predicting shunt response in iNPH than the tap test, as ELDs have PPV, NPV, and accuracy of approximately 1–100%, 36–100%, and 58–100% respectively [68].

Cost/cost-effectiveness

Compared to the tap test, the ELD is relatively more costly as it requires admission to hospital for 3–4 days [72]. However, given the potential morbidity and mortality associated with shunt surgery, it is reasonable to give patients the opportunity to demonstrate response to surgery prior to subjecting them to those risks, and the high PPV of the ELD makes it a reliable measure [70].

Infusion test

Standard procedure

Several variations of the infusion test have been reported, but the fundamental approach is similar [73–75]. Two LP needles are inserted into the lumbar subarachnoid space: the first needle is connected to an infusion pump to infuse artificial CSF (e.g., ringers lactate [76]), while the second needle is connected to a closed-pressure recording device [76]. The patient then either remains in the lateral position, or in some centers, the patient rests on a bed with a fenestration that allows the patient to lie flat with the needles accessible through the opening while the infusion testing is performed [77, 78]. Different methods of infusion are performed, including constant volume or constant pressure [76]. With these techniques, the CSF outflow resistance, R_{out}, or its inverse, CSF conductance, can be calculated. Normal values for the elderly exist [79, 80]. If the patient's CSF outflow resistance is significantly elevated, then shunt surgery is recommended. The test takes 1–2 h to complete and requires specialized equipment and personnel [76].

Contraindications

Similar to the tap test, obstructive hydrocephalus, infection at the insertion site, or coagulopathy are contraindications.

Complications

In a multicenter study of 562 patients who underwent infusion tests, symptoms experienced during the artificial CSF infusion included mild headaches, dizziness, and nausea. Post-LP headache and back pain within the first 24 h of the test occurred in 15% and 13%, respectively [78].

Special points

Infusion testing requires specialized equipment, a protocol, and trained personnel. Infusion tests have a PPV of approximately 75–92% [27, 81]; however, there is variability in the cut-off for R_{out} between studies [73–75].

It has been suggested that a R_{out} of 8 to 18 mmHg/ml/min is associated with the most favorable shunt outcomes [27, 81, 82].

Cost/cost-effectiveness

Compared to the tap test and ELD, the cost of the infusion test probably lies in the middle of the two because, although it may be performed as an outpatient procedure, it requires special equipment and expert staff [70].

Treatment

Natural history of iNPH

Although the pathogenesis of iNPH is not well characterized, the chronic progressive nature of symptoms suggests the disease process likely begins several years prior to presentation. In a population-based prospective 8-year study of 790 elderly individuals (age >60 years old) [83] and a 10-year longitudinal study of 271 individuals (age >70 years old) [84] where subjects underwent brain MRI, 1% had asymptomatic ventricular enlargement with features suspicious for iNPH at the beginning of each study. Over the course of their respective follow-ups, 25 [83] to 30% [84] of those patients with ventriculomegaly had developed clinical symptoms to warrant diagnosis and/or treatment of iNPH. These two studies suggest that ventricular dilation precedes iNPH symptoms by approximately a decade [Level III] [83, 84]. However, there are no guidelines on how to manage patients who present with ventriculomegaly suspicious for iNPH but who lack the clinical symptoms for iNPH. We currently recommend longitudinal follow-up and initiation of pre-surgical testing only when symptoms suspicious for iNPH occur. From a patient-reported symptom perspective, gait disturbance is the earliest and most common symptom of iNPH [10, 23, 24], followed by cognitive impairment [6, 10, 31], then urinary urgency and frequency [6, 10]. However, it remains uncertain how the timing of onset, order, magnitude, and duration the underlying pathological mechanisms of the iNPH phenotype progress prior to patients seeking medical attention.

We recommend patients with a diagnosis of iNPH undergo prompt treatment when possible as the natural history for untreated patients is dismal. Within 6 months of diagnosis, untreated patients undergo significant decline in their functional status (mRS score increases from 2 to 3) and in all iNPH-associated clinical domains (~12-point drop in iNPH scale), including cognition (~3-point in MMSE), gait and balance (~3- and 10-point drops respectively) and continence (~20-point drop) [Level III] [85]. In a review of 4 studies dealing with the natural history of iNPH, Toma et al. reported gait, cognition and continence deteriorated in 23–65%, 42–77%, and 23–59% respectively in untreated iNPH patients over a 3-month–7-year follow-up [86].

Delayed iNPH treatment is associated with worsening of symptoms as early as 3 months following diagnosis [85–87]. In a non-randomized intent-to-

treat trial of 33 iNPH patients, 64% of 14 control patients demonstrated worsened gait and cognitive function from their baseline measures within 3–4 months of follow-up [Level III] [87].

The shunt system

The only effective treatment for iNPH is CSF diversion surgery, which is most commonly achieved with insertion of a shunt system. A shunt system comprises three connected parts: a proximal catheter (tube) which may be placed in the lateral ventricle or lumbar cistern; a distal catheter, which is placed in an absorptive cavity such as the peritoneum or the atrium of the heart; and a valve, which connects the proximal and distal catheters to help regulate the rate of CSF drainage [88]. There are variations in the size and configuration of the end of distal catheters (open vs closed fenestrated) [88]. There are also several types of shunt valves with the most commonly used classified as fixed pressure valves (low, medium, or high pressure) or programmable valves which allow adjustment of the valve opening pressure with a magnet-controlled mechanism [88]. Programmable valves are widely used in iNPH because their adjustability allows tuning of shunt pressure settings to tailor the rate of drainage based on clinical response and complications, without need for shunt revision [88, 89]. It is important to be aware that while iNPH shunt surgery does "decompress" the ventricles to mediate neurological improvement, post-shunt ventricular size is usually not dramatically changed [90].

Proximal ventricular catheter placement

Traditionally, proximal shunt catheters have been passed freehand into the frontal horn of the lateral ventricle. Huyette et al. assessed the accuracy of freehand placement in a retrospective cohort of 97 patients and demonstrated that approximately 44% of freehand proximal catheters were inadvertently placed in regions other than the intended ipsilateral frontal horn, including into extraventricular spaces [Level IV] [91]. In the past 2 decades, several adjunctive techniques have been employed to guide the placement of proximal catheters in order to reduce the risks of catheter-related complications and failure in adult patients. Some of these techniques in adults have included the Headband posterior ventricular catheter guide [92], Wishbone cranial midline marking device [93], and the Ghajar guide [94], as well as framed and frameless stereotactic systems [95–97]. In a prospective multicenter study, Hayhurst et al. showed that electromagnetic-navigated proximal shunt placement reduces poor shunt placement and early failure rate [Level III] [97].

Ventricular and lumbar proximal catheters

In North America and Europe, the most commonly performed shunt surgery for iNPH is VP shunt whereas in Japan and other parts of Asia, LP shunts predominate [41•, 98, 99]. The rate of favorable outcomes of shunt surgery in iNPH ranges from 71 to 90% [Level II–IV] [98, 100, 101]. In an open-label randomized trial (SINPHONI-2), 63% of patients who

underwent LP shunts had favorable outcomes at 12 months [Level III] [41•]. Although VP and LP shunt outcomes appear to be equal in terms of outcomes, the choice of one surgical approach over another seems to be driven by regional or cultural differences [41•, 102]. In a prospective multicenter center study, Miyajima et al. showed that improvement in modified Rankin score and iNPH grading scale [103] were similar between 83 patients with LP shunts when compared to historical data patients treated with VP shunts [Level III or IV] [99].

Distal peritoneal catheter placement

Distal peritoneal catheter problems represent the most common cause of VP shunt failure (90%) in patients with iNPH. Overall, 30–50% of patients will experience shunt failure within the first 2–3 years after insertion [88]. The "standard" peritoneal catheter placement technique (VP or LP shunt) involves insertion of the distal catheter into the peritoneal cavity either via a mini-laparotomy or a trocar conduit. Unfortunately, neither of the two techniques allow for direct visualization of the distal catheter within the peritoneal cavity, which predisposes to a potential risk of bowel perforation, catheter dislodgement, and shunt obstruction. More recently, addition of a laparoscopic approach, which is typically performed by a general surgeon, to place the distal catheter under direct visualization within the peritoneal cavity, is being adopted to mitigate those risks [104, 105•]. In a randomized control trial of 120 patients (60 laparoscopy versus 60 mini-laparotomy) who underwent distal catheter shunt placement, there were no distal shunt failures in the laparoscopy group, whereas 8% of the mini-laparotomy group had distal failures within 12 months of surgery [Level I] [105•]. Peritoneal catheter malfunction occurs secondary to occlusion by omentum, bowel, debris, or intraabdominal fibrous adhesions. To reduce this risk, the distal catheter can be placed away from the omentum, which may be achieved laparoscopically passing the catheter through a small hole placed in the falciform ligament into the paracolic gutter. This procedure also anchors the catheter behind the liver which helps reduce risks of catheter migration [106]. In a consecutive cohort study by Svoboda et al., there were no distal catheter failures in 58 patients who underwent the "falciform ligament technique" [Level IV] [107].

Distal atrial catheter placement

Besides the peritoneal cavity, the distal catheter may be placed in other cavities including the right atrium of the heart (ventriculoatrial (VA) shunts) [108–110], gall bladder [111], and pleural cavity [112, 113]. However, the most common is typically the VA shunt [110, 114]. Early reports of high failure and complication rates with VA shunts[5] have likely contributed to relegation of the VA shunt to second-line therapy that is used when distal catheter placement in peritoneal cavity is not technically possible or has failed [110, 115]. However, enhanced operative techniques with reduced shunt infection rates [116] and use of adjunctive equipment such as fluoroscopy and echocardiography [108, 109], have significantly improved VA shunt complication and failure rates. In a retrospective review

of 150 iNPH patients who underwent VA shunt surgery, Hung et al. reported a 5% distal catheter failure rate over a mean 15 months of follow-up [Level IV] [110]. Recently, transesophageal echocardiography (TEE)-guided distal catheter insertions have gained favorability [114, 117] as they provide 2-dimensional visualization and real-time catheter monitoring of the distal catheter to facilitate precise placement, do not carry risks of radiation and allergic response to contrast, and do not interfere with the surgical field [114]. Although, there are only a few case reports and case series on the use of TEE for VA shunt placement, their results are very promising as TEE is able to significantly reduce distal catheter failures and shunt-related complications [Level IV] [114, 117, 118].

Shunt complications and approaches to prevention

Cardiopulmonary complications due to general anesthesia and postoperative thromboembolic disease are major considerations, but in most circumstances with adequate patient screening and preoperative preparation, they should be uncommon. Serious complications of the shunt insertion procedure should also be low with modern techniques. With the use of neuronavigation assistance, malposition of the ventricular catheter is rare. Inadvertent brain injury or significant tract hemorrhage along the course the proximal catheter is uncommon (<1%). Mild intraventricular hemorrhage is not uncommon (especially in the occipital horns) but is typically not clinically significant. Lung injury due to an inadvertent breach with the tunneling device is possible but very rare. There is also the potential risk to injure intraabdominal contents, particularly viscus perforation and liver injury, all of which are significantly reduced with laparoscopic peritoneal catheter insertion. The infection rate associated with shunt surgery can be kept to less than 2% in iNPH patients when a shunt infection prevention strategy is routinely utilized [116].

Non-shunt surgical techniques

An alternative to shunting is the creation of a shunt-less conduit between the ventricular system and the subarachnoid space. This is typically done with an endoscopic third ventriculostomy (ETV), which involves utilizing a neuroendoscope to make a hole in the floor of the third ventricle to allow passage of CSF into the basal cisterns. However, unlike shunting, which has been consistently shown to be efficacious, the outcomes of ETV have not been favorable for the treatment of iNPH [119–121]. As such, shunting remains the only recommended treatment for patients with iNPH [10, 59, 60].

Non-surgical treatment

Several drug therapies have been explored for the treatment of iNPH [22], but none has yielded consistent results to warrant adoption as pharmacological treatment of iNPH. There are also no specific lifestyle modifications that have been shown to prevent, modify, or treat iNPH. Nevertheless, since majority of the comorbidities identified in iNPH patients respond well to

regular exercising, smoking cessation, and healthy diets [17, 35, 48, 49], it is possible that healthy lifestyle choices may help reduce one's risk for iNPH [49].

Treatment outcomes

Historic reports on the surgical outcomes of iNPH had been highly variable, with good results ranging from 24 to 96% [122, 123]. This has previously generated interesting negative discussions on the efficacy of iNPH treatment and hesitation to accept iNPH as a disease entity separate from other untreatable forms of dementia. However, advances in the past few decades in terms of better understanding of the iNPH disease process, better standardization of iNPH diagnostic and treatment processes arising from the adoption of clinical guidelines for diagnosis, treatment and in research methodologies, and availability of long-term follow-up data, have helped reduce the variations in reported good outcomes to a much improved 73 to 96% [98, 100, 101, 124]. Of the triad, gait is the earliest and most dramatically responsive symptom, and improvement may continue even years after surgery [125, 126]. Cognitive [127, 128] and bladder symptom ([57,74,78,93]) improvement have been reported to occur in 60–80% of patients [129–131]. It is important to consider iNPH as a chronic disease and that patients require life-long longitudinal care to ensure optimization of neurological function. Suspected shunt malfunction should be investigated and if confirmed can be surgically managed with an expectation for restoration of pre-shunt failure neurological condition.

Physical therapy and exercise

Rehabilitation is an important aspect of iNPH treatment, especially in the early stages of recovery following surgery. While rehabilitation programs for other neurological diseases such as stroke, traumatic brain injury, and dementia are effective for iNPH patients following treatment, there have not been any Level I-III studies that have assessed specific programs for their feasibility and effectiveness. Rehabilitation for patients with iNPH should be an interdisciplinary effort and may include physicians, neuropsychologists, nurses, physical therapists, occupational therapists, speech therapists, and recreational therapists. The goal of postoperative rehab is to help improve patients function in four major aspects: gait, cognition, continence, and psychosocial health. However, the goals of any prescribed rehabilitation program must be realistic, taking into account the patients' premorbid functional status, comorbidities, and resource availability. Typically, patients undergo an initial assessment as inpatients to document their level of function following surgery to facilitate decisions on the need, duration, and setting (inpatient vs outpatient) for rehabilitation.

Physical therapy

Usage

The principles and goals of therapy are typically based on geriatric rehabilitation and fall prevention in other well-studied neurological diseases of the elderly such as Parkinson's and Alzheimer's diseases, where Level I and II data are available [132, 133]. The majority of patients require balance and gait exercises commensurate with the severity of dysfunction. The goal of physical therapy is to improve balance and gait quality and safety. However, some patients may require strength exercises to facilitate their recovery of mobility. The physical therapy program should start with an initial evaluation of function and goal setting with the patient. The focus on a specific goal and duration of training may change over time depending on the relative improvement of patients in each domain.

Occupational/neuropsychological therapy

Usage

Occupational therapy addresses issues related to cognition, urinary continence, self-care, adaptability to living environment, and facilitation of compensatory strategies. In some centers, cognitive rehabilitation efforts are administered by neuropsychologists. Cognitive rehabilitation involves exercises that help to improve visual and verbal memory (learning and recall), orientation, attention, speed of information processing, judgment, and self-awareness. Although uncommonly required, speech therapy may be sometimes be required. Urinary continence rehabilitation typically includes toileting programs such as improving toileting times.

Compliance with Ethical Standards

Conflict of Interest

Albert M. Isaacs receives financial support as a graduate student from the Vanier Canada Graduate Scholarship and, recently from the Killam Predoctoral Scholarship programs.
Michael A. Williams currently is a recipient of a research grant from NASA on research on intracranial pressure. In 2017, Dr. Williams received honoraria and paid travel costs from Medtronic Inc. for preparation of independently developed lectures on hydrocephalus, which was presented at Neurosciences Grand Rounds, University of University of Saskatchewan College of Medicine. Dr. Williams is the Chair of the Medical Advisor board of the Hydrocephalus Association (HA). Dr. Williams is a member of the Board of Directors of the HA.
Mark G. Hamilton is a member of the Board of Directors of the HA. Dr. Hamilton received honoraria from Integra (Canada) Inc. for preparation of an independently developed seminar on adult hydrocephalus. Dr. Hamilton is the Chair of the Adult Hydrocephalus Clinical Research Network (AHCRN), Vice-Chair of the Medical Advisor board of the Hydrocephalus Association (HA) and a member of the Board of Directors of Hydrocephalus Canada.

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

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