Idiopathic normal pressure hydrocephalus: an important differential diagnosis

Idiopathic normal pressure hydrocephalus, an uncommon but important differential diagnosis for ataxia, cognitive impairment and urinary incontinence, is surgically treatable, unlike many of its differential diagnoses. This article discusses its assessment, investigation and therapeutic interventions.

Idiopathic normal pressure hydrocephalus is an uncommon but important differential diagnosis to consider in older patients in the presence of cognitive impairment, ataxia and urinary incontinence. It is notable because it is surgically treatable, unlike many of its differential diagnoses. In certain cases, removal or diversion of CSF can ameliorate symptoms and improve function and quality of life. The diagnosis of idiopathic normal pressure hydrocephalus, aside from being incidental on neuroimaging performed for other reasons, relies upon a combination of clinical suspicion and investigation. This review describes the condition, presents an approach to assessment, outlines relevant investigations and evaluates evidence on therapeutic interventions.

Introduction

What is idiopathic normal pressure hydrocephalus and why is it important?

Idiopathic normal pressure hydrocephalus was described by Hakim, under the tutelage of Adams, half a century ago, as a treatable cause of dementia (Adams et al, 1965). In his original studies, Hakim identified a characteristic triad of walking impairment, dementia and urinary incontinence in patients with enlarged ventricles, but normal intracranial pressure. Although the pathophysiology is not fully understood, symptoms are thought to arise from accumulation of CSF. However, recent work has challenged previously held beliefs regarding CSF circulation and absorption. In-vivo imaging of fluorescent markers showed that CSF penetrates the brain parenchyma along paravascular spaces (Iliff et al, 2012). This mechanism enables CSF to act as a lymphatic drainage system and means that pathology affecting small vessels could influence CSF circulation. In light of the fact that cardiovascular risk factors may have an aetiological role in idiopathic normal pressure hydrocephalus (Earnest et al, 1974), there may be a more complicated mechanism at play in its development than previously thought.

Increasingly ageing populations in developed countries change the requirements of health services. In 2010, in America alone, one study estimated that there were 4.7 million individuals aged over 65 years with Alzheimer's disease (Hebert et al, 2013). There is the need for care of older people who are unable to live fully independently, putting an increasing strain on health services. Many of the conditions prevalent in older people are chronic, progressive and irreversible. Idiopathic normal pressure hydrocephalus is an important differential to consider because it can be reversed and intervention can make a significant difference to patients' and their family's lives and also their demands upon health-care resources (Williams et al, 2007; Klinge et al, 2012).

How common is idiopathic normal pressure hydrocephalus?

Normal pressure hydrocephalus can be idiopathic, typically presenting after 60 years of age (Gallia et al, 2006), or can develop at any age secondary to brain insults (secondary normal pressure hydrocephalus) such as subarachnoid haemorrhage (23%), head injury (13%), meningitis (5%), brain tumours and cranial neurosurgery (Meier et al, 1999). True prevalence estimates are difficult to ascertain because of difficulty in diagnosis. Estimated incidence varies widely depending on the population studied and is thought to have a slight male predominance (McGirt et al, 2005). A Norwegian study calculated prevalence of 21.9 per 100 000 and incidence as 5.5 per 100 000, with rates increasing with age. These values reflect minimum rate estimates (Brean and Eide, 2008).

It is difficult to elucidate the proportion of idiopathic normal pressure hydrocephalus patients who have concurrent Alzheimer's disease. Evidence has shown that in cases where idiopathic normal pressure hydrocephalus is accurately diagnosed, improvement after shunt surgery was comparable, irrespective of the presence of concomitant Alzheimer's disease pathology. This suggests that, once idiopathic normal pressure hydrocephalus has been diagnosed, the presence of other diagnoses, such as Alzheimer's disease, should not necessarily in themselves preclude patients from surgery (Golomb et al, 2000).

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How is it diagnosed?

There is no single diagnostic test for idiopathic normal pressure hydrocephalus. Clinical suspicion or incidental findings on neuroimaging for other reasons are the triggers for investigation. For confirmation, a combination of history, examination findings and specific investigations are used, as will be discussed. Hakim's original triad still forms the basis of clinical assessment. Alternative diagnoses for these symptoms must be considered and excluded (*Table 1*) (Gallia et al, 2006). Marmarou et al established evidence-based guidelines in 2005 which are still used today (Marmarou et al, 2005a,b). The diagnosis of idiopathic normal pressure hydrocephalus is classified as probable, possible or unlikely based upon a combination of age, speed and nature of symptoms and CSF opening pressures in conjunction with characteristic changes on imaging. There is no current definition of anatomicopathological changes, because there are limited numbers of autopsy cases in idiopathic normal pressure hydrocephalus.

Clinical assessment

This comprises a thorough history and examination, to assess for differential diagnoses and comorbidities. Relevant investigations should be used to support the diagnosis and inform management, including suitability for surgery.

What is important in the history?

Symptoms

The history should include direct questioning on gait, cognitive and bladder symptoms. The age of onset and symptom timing is important. Gait dysfunction is often the earliest symptom. Suspicion of idiopathic normal pressure hydrocephalus is greater in those who have had symptoms for at least 3 months. Idiopathic normal pressure hydrocephalus classically develops insidiously; if the patient reports a sudden onset of symptoms, alternative diagnoses should be considered (Gallia et al, 2006).

Urinary incontinence usually comprises urgency and frequency with detrusor instability (Sakakibara et al, 2008). It is often misattributed to reduced mobility or age-related functional decline so should be explicitly asked about. A thorough history should cover presence of diabetes, medications such as diuretics, prostatic symptoms in men, and those of stress incontinence in women including gynaecological pathology.

Cognitive impairment has typical frontal deficits, giving psychomotor slowing, impaired attention, verbal fluency and executive function. This is in contrast to Alzheimer's disease in which memory function is predominantly affected. There is also reported deficit in visuospatial and visuoconstructional skills, as well as apathy and poor insight (Devito et al, 2005; Relkin et al, 2005).

Patients may present with the complete triad, but in many cases only one or two symptoms are identifiable. A case series identified gait disturbance in 98%, urinary incontinence in 79%, and cognitive impairment in 78% of patients treated for idiopathic normal pressure hydrocephalus, with the complete triad present in 62% of patients (McGirt et al, 2005).

General medical background

Characteristics of alternative diagnoses should be sought, including history of headaches, neurotrauma, subarachnoid haemorrhage, meningitis or brain tumour which would suggest secondary normal pressure hydrocephalus. HIV dementia is also a differential diagnosis, so questioning relating to risk factors is important. Parkinson's disease is a comparatively common cause of gait disturbance in older people which, like idiopathic normal pressure hydrocephalus, may be associated with neuropsychiatric changes and detrusor instability. Parkinsonian and idiopathic normal pressure hydrocephalus gaits share common features but absence of tremor, rigidity and, particularly, akinesia make Parkinson's disease unlikely. Specific enquiries should be made about any trials of levodopa as idiopathic normal pressure hydrocephalus, unlike Parkinson's disease, is unresponsive to dopaminergic medication.

Aside from assessing baseline functional ability, likelihood of benefit from intervention and suitability for anaesthetic, it is important to enquire about cardiovascular risk factors (hypertension, smoking, family history of cerebrovascular disease, hypercholesterolaemia and diabetes). These have been linked to poor post-shunt outcome (Klinge et al, 2005). There is evidence that patients' ability to withstand surgery, namely their comorbidities,

Table 1. Differential diagnoses for idiopathic normal pressure hydrocephalus

Common	Parkinson's disease
	Alzheimer's disease
	Vascular dementia
	Secondary normal pressure hydrocephalus
	Depression
	Urological bladder condition and neurodegenerative process
Uncommon	Primary gait disorder
	Diffuse Lewy body disease
	Behavioural variant frontotemporal dementia
	Progressive supranuclear palsy
	Vestibular disorders
	Peripheral neuropathy
	Lumbar stenosis
	Arthritis
	Cerebral tumour
	Thyrotoxicosis

correlate with outcome from ventriculo-peritoneal shunting. Use of the Charlson Comorbidity Index suggested that high levels of comorbidity were predictive of poor shunt outcome and may help in determining if a patient is suitable for neurosurgery (Lemcke and Meier, 2012). Use of anticoagulant medications should be noted; although not an absolute contraindication to shunt insertion, they require reversal and temporary cessation before neurosurgery.

What is essential in the neurological examination?

Assessment should aim to demonstrate the characteristics of idiopathic normal pressure hydrocephalus, and rule out common differential diagnoses.

Gait

In idiopathic normal pressure hydrocephalus the gait is characteristically 'magnetic' and typically a slow, shuffling, broad-based ataxia with the feet rotated outwards (Bugalho and Guimaraes, 2007). There is decreased cadence (fewer steps per minute), decreased step length and reduced step height. Patients display en-bloc turning, defined as requiring three or more steps to turn 180° (Relkin et al, 2005). Tandem gait (heel-toe walking) should be assessed. A patient with idiopathic normal pressure hydrocephalus is likely to struggle and correct him-/herself at least twice for every eight steps.

Upper and lower limbs

Often in idiopathic normal pressure hydrocephalus, examination of the patient's legs is normal when supine, in contrast to the poor performance when standing or walking. Increased tone or cogwheel rigidity raises suspicion of Parkinson's disease. Assess for focal deficits, suggestive of a brain tumour or stroke. In idiopathic normal pressure hydrocephalus tendon and plantar reflexes are usually normal. Idiopathic normal pressure hydrocephalus does not normally impair coordination. Sensory impairment, including proprioception, is not a feature of idiopathic normal pressure hydrocephalus.

Cranial nerves

Fundoscopy is normal in idiopathic normal pressure hydrocephalus; papilloedema may be seen in cases of secondary normal pressure hydrocephalus, or hypertensive retinopathy suggestive of vascular dementia.

Cognitive function

Mini mental state examination is a validated, replicable test of function. Of note, in a cohort of patients who were given shunts, those who were within the 'demented' range (<24/30 on the mini mental state examination) preoperatively were all within the non-demented range postoperatively (Iddon et al, 1999). Referral for formal neuropsychiatric testing may be considered. Alzheimer's disease should be considered as a differential, as should dementia with Lewy bodies – particularly in the presence of rigidity, tremor and visual hallucinations. Vascular dementia is also common in these populations and should be considered, as should depression manifesting as pseudodementia. Use of other tests such as Rey Auditory Verbal Learning Test, Stroop test and Grooved Pegboard have all been shown to be diagnostically sensitive, with the latter two more sensitive to treatment effects (Hellström et al, 2012b).

Urinary function testing

Formal testing is not routinely recommended unless other diagnoses are being pursued.

An idiopathic normal pressure hydrocephalus scale has been proposed which amalgamates the aforementioned components and scoring systems. It covers the domains of gait, neuropsychology, balance and continence and would enable repeated testing over time and across trials, although it is relatively untested as yet (Hellström et al, 2012a).

Referral and specialist investigations

Patients with idiopathic normal pressure hydrocephalus may be found in secondary services through a variety of specialities: geriatrics, psychiatry, urology, uro-gynaecology, orthopaedics, neurology or neurosurgery, depending on the patient's presentation and local referral pathways.

It is vital to rule out differential diagnoses and secondary normal pressure hydrocephalus through investigations. Concurrent urinary tract infection should be excluded via urine analysis and, if appropriate, microscopy, sensitivity and culture of a midstream urine sample. In addition, blood samples should be sent for coagulation and a 'confusion' screen: full blood count, white cell count, coagulation, inflammatory markers (C-reactive protein, erythrocyte sedimentation rate), thyroid function tests, vitamin B_{12} and folate levels, and syphilis serology. There are no routine investigations for Parkinson's disease as this is a clinical diagnosis. In cases where the tremor symptoms are atypical and there is uncertainty distinguishing Parkinson's disease syndromes from essential tremor, dopamine reuptake scans may rarely be considered. They are not routinely used, however, and do not have a role within assessment for idiopathic normal pressure hydrocephalus.

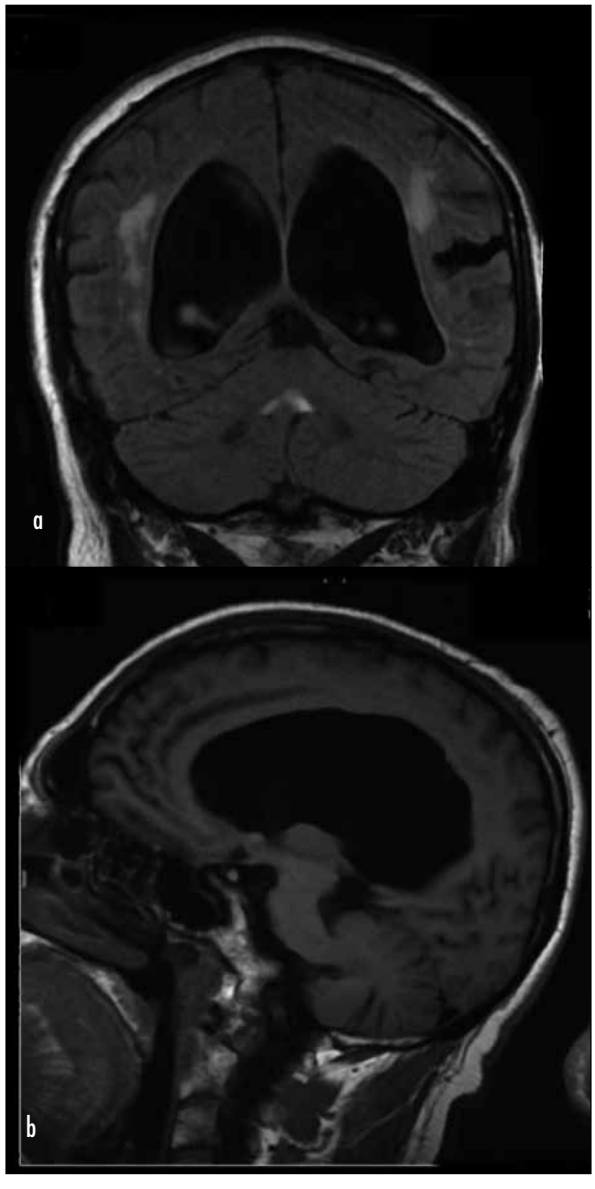
Initial investigation will involve neuroimaging: either magnetic resonance imaging or computed tomography (*Figures 1* and *2*). In idiopathic normal pressure hydrocephalus enlargement of the lateral ventricles is seen, typical of a communicating hydrocephalus, which is disproportionate to the degree of cortical atrophy, with periventricular CSF transudation and, on magnetic resonance imaging, an aqueductal flow void (Gallia et al, 2006). An Evans' ratio may be used as a criterion for idiopathic normal pressure hydrocephalus and is calculated by dividing the maximum width of the ventricular frontal horns on imaging, by the largest (biparietal) skull

diameter. Values greater than 0.3, considered in the clinical context, may be indicative of idiopathic normal pressure hydrocephalus (*Figure 3*).

CSF investigations

After neuroimaging, additional specialist CSF hydrodynamic procedures are used to increase diagnostic certainty and help predict shunt responsivity (Boon et al, 1997). There is not one single test which is diagnostic, rather a combination are needed dependent on the findings (Marmarou et al, 2005a), for example a lack of response to lumbar CSF drainage may lead to an external lumbar drain being trialled.

Figure 1. a. Coronal T2 fluid-attenuated inversion recovery magnetic resonance imaging of patient with idiopathic normal pressure hydrocephalus showing ventriculomegaly and periventricular hyperintensities. b. Sagittal T1 fluid-attenuated inversion recovery magnetic resonance imaging of the same patient, with thinning (bowing) of the corpus callosum.



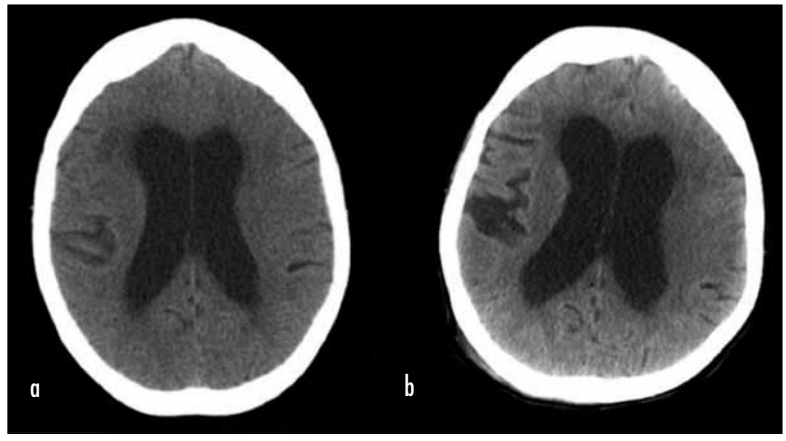
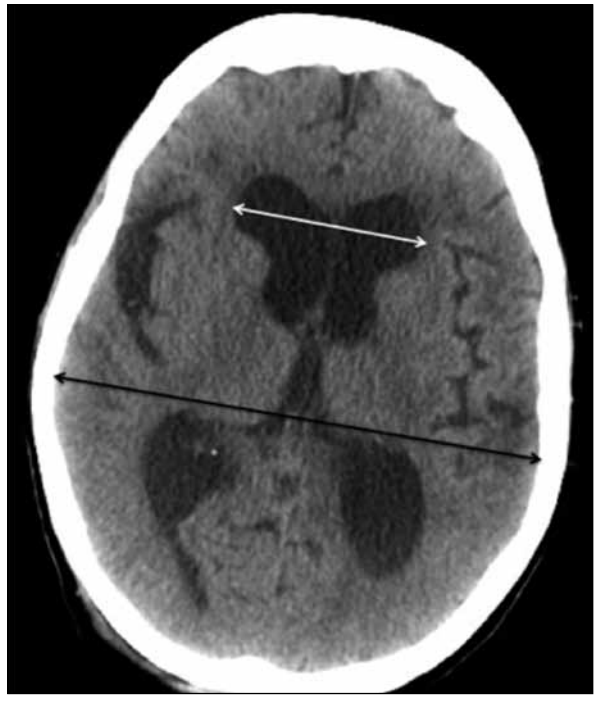


Figure 2. Axial computed tomography scan of the head from the same patient (a) taken in 2007 and (b) taken in 2012, showing ventriculomegaly with minimal sulcal enlargement. The patient underwent significant symptom progression despite relatively minor computed tomography changes during this period of time. Note the rounded appearance of the frontal horns. The enlarging right lateral hypodensity may reflect transependymal CSF spread. A shunt was inserted following the 2012 scan.

The simplest of these procedures is the CSF tap test, which involves assessment of symptoms before and after withdrawal of 30–50 ml of CSF via lumbar puncture. Patients whose symptoms improve after drainage, and this may last for weeks or even months, are considered promising candidates for shunt surgery (Marmarou et al, 2005a). However, the test has been shown to have poor sensitivity (26–61%)(Marmarou et al, 2005a). Patients with high opening pressures should be investigated for secondary causes of normal pressure hydrocephalus. CSF

Figure 3. Calculation of Evan's index showing maximum ventricular frontal horn width (white arrowed line) divided by the maximum calvarial width (black arrowed line).



samples should also be sent for analysis of cell count, protein and glucose as chronic meningitides such as cryptococcal meningitis can masquerade as normal pressure hydrocephalus.

A more definitive test is the lumbar infusion study, which has been approved for the investigation of suspected idiopathic normal pressure hydrocephalus in the UK by the National Institute for Health and Clinical Excellence (2008). It involves infusion of fluid at a fixed rate into the epidural space while monitoring outflow resistance. Various numerical cut-off values are used to assess the likelihood of responsiveness to shunt surgery. This test has a sensitivity of 57–100% and positive predictive value of 75–92% (Marmarou et al, 2005a). A European multicentre study of 115 patients who had ventriculo-peritoneal shunts inserted for normal pressure hydrocephalus correlated investigative readings with scores of symptoms pre- and postoperatively and found that CSF tap test and infusion studies both had good predictive value, of >90%, but were not useful in excluding patients from shunting. This means that further tests are needed to assess poor responders to these tests (Wikkelsø et al, 2012).

Prolonged external CSF drainage for 1–5 days via an indwelling externalized lumbar catheter (lumbar drain) has a sensitivity of 50–100% and good positive predictive value of 80–100% (Marmarou et al, 2005a). This is preferred by some as it enables ongoing inpatient symptom assessment with CSF drainage. Continuous CSF pressure monitoring and analysis of waveforms such as nocturnal pulse pressure can also be used to inform management decisions (McGirt et al, 2005).

Table 2. Signs and symptoms of shunt malfunction – all require neurosurgical advice

Over-drainage	Symptoms and signs: postural headache (worse on patient being upright, relieved by lying). Computed tomography may show subdural hygroma
	Management: the shunt valve can be replaced by a programmable one with high resistance or anti-siphon settings, or the shunt tied off and the patient observed
Under-drainage	Symptoms and signs: limited symptomatic improvement
	Management: Check patient is not constipated or gaining weight as this can increase intra-abdominal pressure and prevent adequate drainage. Patency of the shunt system needs to be examined, and if the shunt is draining, a lower resistance or programmable valve could be inserted and settings adjusted to improve drainage
Shunt infection	Symptoms and signs: fever, meningism, symptomatic deterioration, raised white cell count, tenderness or erythema over shunt tubing in neck, chest or abdomen
	Management: CSF samples for microbiological diagnosis, antibiotics, potential shunt revision
Seizures	Symptoms and signs: seizures may be focal or generalized and can occur once or form part of a seizure disorder
	Management: Computed tomography of the head, and anticonvulsants

There are no CSF markers that currently fulfil the necessary criteria for clinical use as biomarkers in the diagnosis of idiopathic normal pressure hydrocephalus. This is an area of continuing research (Tarnaris et al, 2009).

Management options

Following positive investigation findings, the options for management range from supportive to surgical intervention. It is possible to use medical management with repeated lumbar punctures and use of acetazolamide to decrease CSF production, but these are often bridges to surgery and not suitable long term. The appropriateness of surgical intervention must be weighed up, as with any surgical procedure. This involves a case-by-case analysis of the patient's likelihood of response, balanced with the possibility of complications such as infection and mechanical failure. It is not a small undertaking to decide to operate and will involve a multidisciplinary discussion. Below are discussed the neurosurgical interventions available, followed by analysis of evidence for the various options.

Shunting

The mainstay of surgical treatment is CSF diversion. The shunt comprises silicone-based silastic tubing connected by a one-way valve directed caudally, normally to the peritoneal cavity but also to the pleural space or right cardiac atrium. Shunts are inserted into the frontal or occipital horn of the lateral ventricle of the non-dominant, right cerebral hemisphere, and shunt valves can be palpated either above or behind the ear, under the scalp. Programmable valves have largely superseded fixed medium–low pressure valves in idiopathic normal pressure hydrocephalus, reducing the risk of subdural hygromas. Settings of the flow rates and pressure at which CSF is drained can be titrated to optimize symptom relief by the application of a programming magnet to the scalp. This can easily be done as an outpatient. After discharge, the patient will require monitoring for shunt-related complications (*Table 2*).

Endoscopic third ventriculostomy

An alternative to CSF shunting is endoscopic third ventriculostomy (Kandasamy et al, 2012). This involves fenestration of the floor of the third ventricle to provide an alternative pathway for CSF drainage. While typically used for obstructive hydrocephalus, it has had some success in idiopathic normal pressure hydrocephalus, a communicating hydrocephalus. A recent randomized study found those who underwent ventriculo-peritoneal shunt had significantly better functional neurological outcome 12 months postoperatively than those who underwent endoscopic third ventriculostomy (Pinto et al, 2013). Further studies comparing efficacy in the long term are needed, and individual patient circumstances should be taken into consideration, for example anatomical varia-

tion and suitability for neuroprosthesis implantation. The authors' opinion is that shunting confers more aggressive symptom reversal and thus more complete restoration of function.

What is the evidence for efficacy of surgical intervention *vs* conservative management?

There are no randomized controlled trials comparing efficacy of CSF surgical intervention for idiopathic normal pressure hydrocephalus *vs* placebo or conservative management (Klinge et al, 2005). Furthermore, existing study outcomes are difficult to interpret because of differences in inclusion criteria, follow-up duration and outcome measures. Improvements have been reported in nearly 60% of patients shunted, with just under half of these having prolonged improvement. However, complications were reported in 38% of patients and 6% had permanent neurological deficit or death. This retrospective analysis also highlighted that there was no correlation between degree of hydrocephalus and response, but presence of the full symptomatic triad was suggestive of shunt responsiveness (Hebb and Cusimano, 2001).

A large study of symptoms in 252 patients suggested that gait improved most commonly (81%), followed by cognition (64%) then urinary incontinence (56%) (Cage et al, 2011). It is also thought that early treatment in patients with mild symptoms has the best prognosis. Studies with longer follow-up periods have found that improvements are only sustained in 25–47% of patients over 3–5 years of follow up (Malm et al, 2000; Klinge et al, 2005). It is not clear whether deterioration is caused by progression of idiopathic normal pressure hydrocephalus or the influence of comorbidities, since a number of studies have shown that worse outcomes are associated with the presence of pre-existing cardiovascular and cerebrovascular disease (Malm et al, 2000). The aetiological role of cardiovascular and cerebrovascular disease in the development of idiopathic normal pressure hydrocephalus requires further exploration (Earnest et al, 1974). A 12-month European multicentre trial noted that the number of people able to live independently after shunting had increased from 53% to 82% post-shunting (Klinge et al, 2012), adding weight to the benefits of shunting.

When to operate?

The above mentioned European study, spanning 13 different centres, used symptoms, signs and magnetic resonance imaging findings compatible with idiopathic normal pressure hydrocephalus alone for diagnosis. All patients who fulfilled these criteria went on to have a shunt irrespective of CSF tap test and lumbar infusion study results; 84% of this selected group had significant improvement postoperatively when assessed by the modified Rankin Scale and new idiopathic normal pressure hydrocephalus grading scale. This lends huge support to clinical judgment in determining which patients to shunt (Klinge et al, 2012). Increased knowledge and awareness of the phenotype may be contributing to the high success rate in the absence of invasive investigation, but this requires further evidence before such CSF investigations are abandoned.

A mathematical analysis of patients with moderate dementia, who have a limited number of quality-adjusted life years, questioned whether shunt placement should be considered more widely. They suggested that a ventriculo-peritoneal shunt should be considered in more patients with suspected normal pressure hydrocephalus because of the potential to increase the average 1.4 quality-adjusted life years in a 65-year-old with dementia, by 1.7. This is controversial because of the invasiveness of the procedures and potential complications, and is also only a mathematical model, but is interesting as it further questions the level of diagnostic certainty needed before surgically intervening (Stein et al, 2006).

Decisions to operate require specialist multidisciplinary input. Current literature suggests that there is a role for surgical intervention and that it can be of great benefit to patients and their families. However, there remain challenges in patient selection and also in maintenance of the benefit of shunting over longer periods.

Conclusions

Idiopathic normal pressure hydrocephalus, although uncommon, is an important differential diagnosis for gait disorders, cognitive decline and urinary dysfunction in older people and as such should be borne in mind on these presentations because of the potential for reversibility by CSF diversion. Many aspects of the condition remain incompletely understood including the underlying pathophysiology, true prevalence and how to select patients who will benefit the most. This review increases awareness of this differential by clinicians working with older patients, so as to give those who might gain some return of function a chance at improving their quality of life (Klinge et al, 2012). BJHM

Conflict of interest: none.

KEY POINTS

- Idiopathic normal pressure hydrocephalus is a recognized cause of gait disorder, cognitive impairment and urinary incontinence in older people.
- Idiopathic normal pressure hydrocephalus is an important diagnosis to consider, as neurosurgical intervention can produce dramatic symptomatic relief.
- Clinical history and examination should raise suspicion of the diagnosis.
- Subsequent action includes exploration and exclusion of differential diagnoses, baseline blood tests, neuroimaging and further hydrodynamic investigations.
- Standard surgical management involves CSF diversion by ventriculoperitoneal shunt insertion.

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