

We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

4,800

Open access books available

122,000

International authors and editors

135M

Downloads

Our authors are among the

154

Countries delivered to

TOP 1%

most cited scientists

12.2%

Contributors from top 500 universities



WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.

For more information visit www.intechopen.com



Idiopathic Normal Pressure Hydrocephalus: An Overview of Pathophysiology, Clinical Features, Diagnosis and Treatment

Rubesh Gooriah and Ashok Raman

Additional information is available at the end of the chapter

<http://dx.doi.org/10.5772/64198>

Abstract

Normal pressure hydrocephalus is characterised by the triad of gait disturbance, dementia and urinary incontinence. Although our understanding of the condition has considerably improved since it was initially described over 50 years ago, its pathophysiology is still a matter of debate. We provide an overview of the current concepts in pathophysiology and discuss the clinical features, diagnosis and treatment of this cause of dementia.

Keywords: cerebrospinal fluid, cerebral blood flow, vascular compliance, CSF outflow resistance, neurodegeneration

1. Introduction

First described by Hakim and Adams [1] in 1965, normal pressure hydrocephalus (NPH) is a potentially reversible cause of dementia. It is a communicating hydrocephalus, which occurs as a result of impaired re-absorption of cerebrospinal fluid (CSF). This can be caused by a number of conditions including meningitis, trauma and subarachnoid haemorrhage. However, in a large number of cases, it is idiopathic (INPH). INPH is characterised clinically by the triad of gait disturbance, cognitive decline and urinary incontinence. Ventriculomegaly is observed on magnetic resonance imaging (MRI) or computed tomography (CT). However, the symptoms of INPH are non-specific and can occur in other conditions. Moreover, the classic triad is not always present. Varying combinations and degrees of each element of the triad are encountered in different patients and depending on the stage of the condition. INPH has an

insidious onset and progresses gradually. Shunt surgery results in a positive response in as many as 84% in a European multicentre study [2]. Although the treatment is surgical, neurological input is important for the diagnosis and identification of suitable shunt candidates. In some countries, hydrocephalus is a purely surgical condition. However, like several authors, we believe that a multidisciplinary approach is essential for the optimal management of these patients. In our neuroscience centre, the management of INPH involves the neurologists, neurosurgeons and physiotherapists.

2. Methods

This review was prompted by the large number of publications on INPH. We searched the databases of Medline, Embase and the Cochrane Library for articles relating to INPH up to February 2016. We included review articles and research studies according to their relevance.

3. Epidemiology

It is difficult to accurately establish the incidence and prevalence of INPH because several cases are likely to be undiagnosed due to the non-specific nature of the symptoms. However, it is clear from epidemiological studies that the incidence increases with age. Tisell et al. [3] observed that one to two shunt operations per 100,000 inhabitants were being performed yearly for INPH. Brean and Eide [4] found that the prevalence was up to 181.7 per 100,000 people in the 70–79 years age group in Norway [4]. After randomly subjecting 497 individuals over the age of 65 to magnetic resonance imaging (MRI) of the brain, Tanaka et al. found a prevalence of 1.4% in that age group [5]. It is also estimated that up to 10% of patients with dementia may have INPH [6].

4. Pathophysiology

The CSF space is a dynamic pressure system. It is responsive to changes in CSF formation or reabsorption rates, arterial and venous flow, compliance of the intracranial structures and fluctuations in intracranial pressure (ICP). Around 500 ml of CSF is produced every day and the total volume of CSF at any one point is between 120 and 150 ml. The brain is unique in the sense that it is the only organ enclosed in a non-expansile box (i.e. the skull). According to the Monro-Kellie hypothesis, the total volume of the constituents in the cranium is fixed. Therefore, an increase in the volume of any of the constituents has to be matched by a decrease in the volume of another to avoid an increase in intracranial pressure. The volume of blood entering the brain varies with the cardiac cycle. There is a net intracranial inflow of blood during systole and a net outflow during diastole. Arterial supply to the brain is pulsatile whereas venous flow is less so, and this mismatch causes transient rises in pressure. The brain

and other intracranial constituents can compensate for this in two ways. Firstly, the blood vessels have a degree of compliance which allows for a smoother influx of arterial blood. Secondly, CSF flows back and forth through the cerebral aqueduct in response to pulsatile blood flow, thereby maintaining intracranial pressure stable. However, in INPH, the intracranial constituents become less compliant [7]. A reduction in vascular compliance especially in the superior sagittal sinus has been found [8]. This can initially be countered by increased pulsatile CSF flow through the aqueduct. If this fails, the amplitude of arterial pulsatility increases during systole inducing large ICP pulsations ('water hammer' effect). These pulsations, in addition to causing venous damage in the periventricular region, displace the brain towards the skull [9]. Hydrocephalus occurs as a result of enlarging ventricles at the expense of a reduced subarachnoid space. This is secondary to increasing pressure within the ventricles directed towards the subarachnoid space. The pressure gradient arising between the ventricles and the subarachnoid space is termed 'transmantle pressure'. The transmantle pressure gradient has to be the only force which could cause such changes to the brain [9]. CSF spaces revert to normal following shunting, implying that the transmantle pressure gradient can be reduced or reversed. This pressure gradient also explains why, although there is increased intraventricular pressure, the measured opening pressure during a lumbar puncture is within normal limits. It also implies that 'normal pressure' in NPH is somewhat of a misnomer.

What triggers the initial reduction in compliance that results in INPH? Most theories on INPH attempt to explain the pathophysiology around the finding of reduced cerebral blood flow (CBF). There is a strong association between impaired CBF and INPH. Patients with INPH are more likely to have concomitant cerebrovascular disease [10]. MRI shows increased white matter changes (WMCs) [11] and this is further supported by neuropathological studies showing microvascular infarctions but also interstitial oedema, ependymal disruption, gliosis and neuronal degeneration [12, 13]. In addition, there is an association between high ICP and impaired cerebrovascular autoregulation [14]. Age-related atherosclerosis has been proposed as being responsible for the reduction in vascular compliance [15]. This would explain the association between NPH and vascular disease (VD). Bateman [8], on the other hand, proposes that increased transvenular resistance in the territory of the superior sagittal sinus is the initiating event in NPH. While some consider that CSF resorption occurs at the level of the arachnoid villi or arachnoid granulations, others believe that the majority of CSF resorption occurs through brain parenchyma at the levels of capillaries and veins [9, 16–18]. If the latter hypothesis is true, CSF resorption would be affected with increased transvenular resistance. Indeed, CSF resorption is unequivocally abnormal in INPH [19]. CSF outflow resistance or conductance (which is inversely proportional to resistance) has been investigated in a few studies [20–22] and found to be impaired. Early studies in animals and humans suggest that, in the initial stages, mounting CSF intraventricular pressure secondary to abnormal CSF flow causes ventricular dilatation [8]. It is therefore possible that CSF outflow disturbance, occurring secondary to reduced venous compliance, is directly related to the ventriculomegaly seen in INPH.

But why would venous resistance increase in an elderly patient? Bradley believes that deep white matter ischaemia is the triggering event [23]. Due to ischaemia, surrounding arterioles

are already maximally dilated, and this would explain the loss of autoregulation [23]. When the arterioles are obstructed, venous collapse ensues, followed by impaired CSF drainage and ventricular enlargement [23]. The problem we have with this hypothesis is that if one wants a unifying theory with ischaemia as the initiating trigger, one would struggle to explain the appearance of NPH in disorders such as progressive supranuclear palsy (PSP), corticobasal degeneration (CBD) and Alzheimer's disease (AD). Periventricular white matter ischaemia is an uncommon finding especially in PSP and CBD. Yet, there has to be a final common pathway which results in hydrocephalus in all these conditions. We hypothesise that neurodegeneration has a role to play in INPH, at least in some cases. The following findings would support this:

- Of the 38 patients in two studies who were diagnosed with INPH, vascular changes (71%), AD (61%), PSP (2.6%) and CBD (2.6%) were the most frequent co-existing pathologies and none had specific neuropathological changes to suggest INPH as an entity [24, 25].
- Levels of tau protein in CSF, an index of neuronal degeneration, were found to be higher in patients with NPH compared to healthy controls [26] although phospho-tau181 was lower in INPH than in those with established AD [27].
- Midbrain atrophy is strongly associated with gait disturbance in NPH [28].
- Although the gait disturbance improves with shunting, the dementia seen in INPH often does not and it continues to progress, suggesting a difference in the aetiopathogenesis underlying these symptoms.
- Even if there is an initial response, overall the condition eventually progresses despite a functioning shunt in situ in the majority of cases. It is therefore possible that those who deteriorate quicker also have more rapid neurodegeneration (e.g. PSP) than those who deteriorate less rapidly (e.g. AD).

Finally, we take the opportunity to emphasise the possibility that INPH has different causes which form a pathophysiological continuum. This would not only explain the differences with shunt response and rates of progression but would also explain why a universal theory remains elusive. It would perhaps be more appropriate to refer to these conditions, where known, as VD-associated NPH, AD-associated NPH, etc.

5. Clinical features

5.1. Gait disturbance

Gait disturbance is usually the commonest and earliest symptom of INPH. Its onset is insidious over months and sometimes years. It is also the one that is most likely to respond to shunting. The gait impairment in NPH is frequently described as 'apraxic'. Other descriptors used are 'shuffling', 'magnetic' and 'broad-based'. Thompson [29] is in favour of the term 'frontal lobe ataxia' instead of gait apraxia, which is defined as an impairment of gait not attributed to motor or sensory deficits, although he acknowledges that this is based on observation rather than on firm evidence for this. Interestingly, some patients display normal ability to move the legs in

a recumbent position while being practically unable to walk. This phenomenon indicates that the gait disturbance is due to a problem with locomotion rather than a pure motor dysfunction. There is no single feature that is pathognomonic of the gait disturbance in NPH. In mild cases, patients may display a broad-based gait but in more severe cases there is a reduction in stride length [30]. The feet appear clumsy and there is difficulty initiating foot movements. Patients are also slow to rise from a seated position. The gait is also characterised by reduced step height and a typical disturbance of the dynamic equilibrium [31]. About 30% of patients experience freezing of gait [31]. Patients tend to turn in multiple small steps. Postural instability and falls are common. The gait pattern in INPH is visibly different from that of Parkinson's disease [31]. A wider step, as well as increased foot angles, is uncharacteristic of Parkinson's disease but common in INPH. Upper limb movements are preserved. The reason is that the motor fibres controlling the upper extremities and face originate more laterally in the motor cortex and are subsequently subjected to less stretching due to hydrocephalus [32]. Upper motor neuron signs, such as spasticity and hyperreflexia, are unusual. Since the symptoms of INPH are symmetrical, any lateralising signs should raise suspicion of other disorders.

5.2. Dementia

The cognitive deficits in INPH are classically that of a subcortical dementia with predominantly frontal features [33–35] and are characterised by apathy, inattention, psychomotor retardation and poor executive function [36]. It is worth noting that the term 'dementia' is used to designate the cognitive impairment in INPH although some patients who present early may not have evidence of this or may not meet the criteria for dementia on cognitive testing. Saito et al. have shown that the deficits extend beyond executive function, attention and memory to visuospatial and visuospatial domains on neuropsychological testing [37]. There is substantial overlap between INPH and AD but frontal lobe dysfunction account for >50% of the cognitive deficit in INPH while memory impairment is responsible for >50% of the cognitive deficit in AD [37]. The degree of neuropsychological impairment in INPH has also been found to relate to the severity of other signs of INPH [38]. Those with vascular risk factors performed worse than those without [38]. Compared with Binswanger's disease, impairment of memory and visuospatial attention in NPH may be more pronounced [39].

5.3. Urinary incontinence

Urinary incontinence is often the last symptom to appear, although it is well established that each symptom can occur independently of the others [40]. Increased urinary urgency occurs earlier and is almost always present in INPH [40, 41]. Urinary incontinence is also very common in the elderly and therefore, on its own, lacks specificity. Fisher [40] considered it to be a frontal lobe incontinence as patients were indifferent regarding where and when to urinate. This correlates with the pattern of cognitive deficits mentioned earlier. Sakakibara et al. [42] have found that detrusor overactivity, seen in 95% of their cases, is fundamental to the appearance of urinary urgency, frequency and incontinence. Seventy-one per cent had voiding symptoms such as difficulties in initiating urination and poor flow [42]. Bladder dysfunction can improve after shunting suggesting that the symptoms are likely secondary to impaired

cerebral control of bladder storage. The underlying mechanism for detrusor overactivity in patients with NPH appears to be related to reduced cerebral blood flow in the right frontal cortex, and to a lesser extent impaired basal ganglia function [43]. Reduced mobility could also be contributing to incontinence in these patients [43].

6. Investigations

6.1. Neuroimaging

The diagnosis of INPH in the right clinical context relies on the finding of hydrocephalus on brain imaging (**Figure 1A**). Hydrocephalus is not synonymous with ventriculomegaly. Although ventriculomegaly is commonly found in the elderly population, this does not imply the presence of NPH. In NPH, the ventriculomegaly is typically out of proportion to the amount of atrophy present. CT of the brain is a sensitive imaging modality to identify NPH but MRI provides additional information such as aqueductal stenosis, white matter changes or the presence of an underlying aetiology (e.g. AD). A coronal section reveals a narrow subarachnoid space surrounding the outer surface of the brain (hence the term 'tight convexity') and narrow medial cisterns. The cortical sulci at the vertex are effaced (**Figure 1B**), whereas the temporal horns are widened (**Figure 2A**). The third ventricle is often enlarged, whereas the fourth ventricle can be either dilated or normal. Therefore, a normal-sized fourth ventricle in the presence of enlarged lateral and third ventricles does not necessarily suggest aqueductal stenosis and is a finding consistent with NPH. Other imaging features of NPH are discussed below.

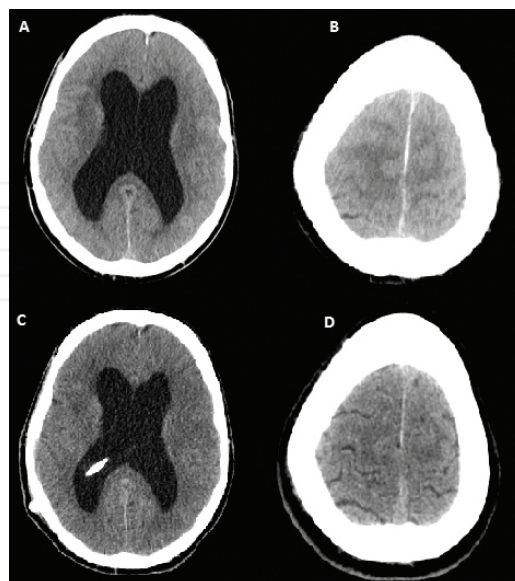


Figure 1. Ventriculomegaly and effacement of sulci at the vertex in a patient with INPH (**A** and **B**), with some post-operative improvement (**C** and **D**).

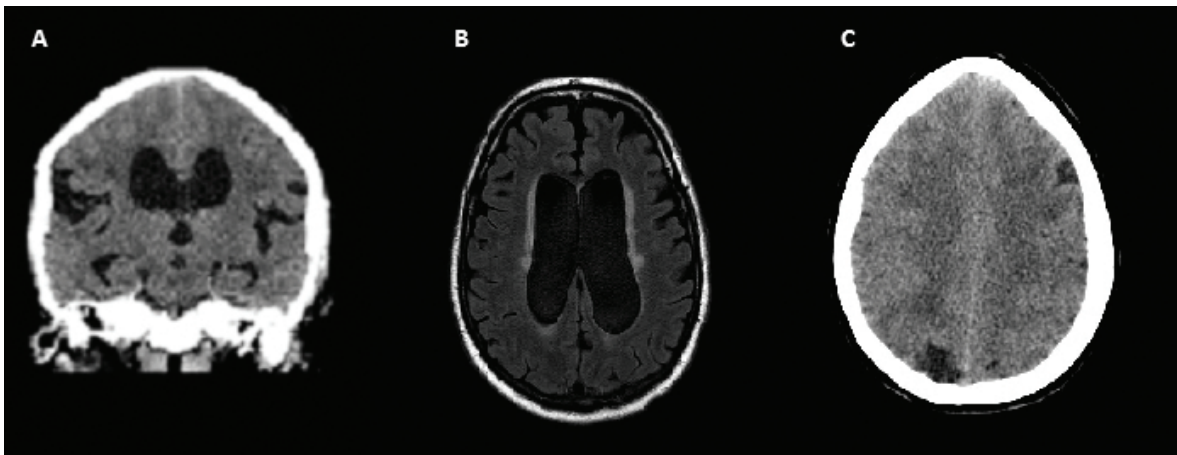


Figure 2. (A) Dilated Sylvian fissures and temporal horns. (B) Periventricular white matter hyperintensities on MRI. (C) Isolated dilated sulci.

6.1.1. *Evan's index*

An objective way of assessing whether the ventricles are enlarged is through the use of Evan's index. It is the ratio of the maximum width of the frontal horns of the lateral ventricles and the transverse inner diameter of the skull, measured at the same level on both axial CT and MRI images [44, 45]. A value above 0.30 is considered significant, although in our own experience, the higher the value, the more specific it is for NPH. Unfortunately, Evan's index is a crude marker of hydrocephalus and varies significantly depending on the location and angle of the slice [46]. It is therefore of limited value on its own.

6.1.2. *Callosal angle*

The concept of callosal angle with respect to NPH was first described on pneumoencephalogram by Benson et al. [47] and thereafter by Sjaastad and Nordvik [48]. The International guidelines mention an angle of greater than 40° as supportive of NPH [49]. However, using MRI, Ishii et al. [50] found that a callosal angle of less than 90° , measured on a coronal plane, which is perpendicular to the AC-PC plane on the posterior commissure plane, helped in differentiating INPH patients from AD and normally aged subjects. The narrow angle is caused by the elevation of dilated ventricles and compression due to dilated Sylvian fissures (**Figure 2A**). When combined with Evan's index of >0.3 , INPH could be discriminated from AD with a sensitivity and specificity of 97 and 94%, respectively [50].

6.1.3. *White matter changes (WMC)*

INPH is known to be associated with deep white matter changes (DWMC) and smooth periventricular hyperintensity (PVH) [51] on MRI (**Figure 2B**). As discussed earlier, there is an element of cerebral hypoperfusion in INPH which is thought to contribute to the development of INPH. It is, however, unclear whether the WMC are cause or effect. Regardless of the underlying pathophysiological mechanisms implicated in NPH, there is consistent neuropa-

thological evidence demonstrating the involvement of white matter. A diversity of pathological observations, such as direct mechanical compression of the periventricular white matter, ischaemic demyelination and infarction, have been noted in INPH [12, 13, 52]. Indeed, DWMC and subcortical infarctions are commonly seen in patients with Binswanger's disease, and these patients often have similar symptoms to those with INPH. Tullberg et al. [51] evaluated the diagnostic features of DWMC and PVH using MRI, and found that no MRI variable could reliably differentiate NPH from BD. One explanation for this result, put forward by the authors, is that NPH and BD are two disorders with similar pathophysiological mechanisms or that they form a pathophysiological continuum of increasing microangiopathy [51].

6.1.4. CSF flow void

As mentioned earlier, CSF flows back and forth the aqueduct during the cardiac cycle in response to arterial blood flow to the brain. This was initially observed as a flow void, consisting of a decreased MRI signal, mainly in the aqueduct on T2-weighted images of early MR scans in patients with communicating hydrocephalus [53–55]. CSF flow void can be observed in normal individuals, but it is more prominent in INPH [56]. Increased aqueductal CSF flow initially appeared to be predictive of a good response with shunting [55, 57, 58], but further studies have found poor correlation between the extent of CSF flow void and surgical outcome [56, 59].

6.2. CSF tap test

Patients with suspected INPH, based on clinical features and neuroimaging, should undergo a high-volume CSF tap to predict response with shunting. The rationale for a CSF tap is that it simulates the physiological effect of a shunt [45]. The patient is assessed pre- and post-CSF tap for gait and cognitive improvements. About 40–50 ml of CSF is usually removed. Gait is most likely to ameliorate following CSF tap; therefore, it is the best indicator of response. In our centre, we use the 10-m timed-walk test and Tinetti test to assess gait and balance before and after CSF removal. Our patients are also consented for video recordings as these can be useful to retrospectively assess patients especially when the improvement following CSF tap is not clear. It is common that some patients or their carers only notice an improvement a couple of days down the line. We therefore carry out follow-up telephone assessments in all our patients 3 days after they have undergone a CSF tap. This is quite a subjective measure for improvement. Nevertheless, it reduces the chances of missing potentially suitable candidates for shunt surgery. Unfortunately, although the CSF tap test has a high positive-predictive value for shunt success, it has a low sensitivity [60] and should not be used to exclude patients from shunt surgery. There are patients who do respond to shunt surgery after a negative tap test. The first edition of the Japanese guidelines advocated repeating the tap test if initially negative [61], but the more recent edition suggests that further investigation may be required [62]. Recently, Yamada et al. have shown that the timing of the CSF tap affects the accuracy of the test [63]. It should be carried out as soon as symptoms appear [63]. An external lumbar drain, which provides continuous drainage, has a similar predictive value to the CSF tap test, a higher

sensitivity [64, 65], but a low negative-predictive value. It is important to note that this test is more invasive, and can give rise to complications such as radicular pain and meningitis.

7. Diagnostic guidelines

Different centres use different criteria for diagnosing INPH and recommending shunt surgery. The decision to shunt a patient with predominantly gait disturbance, typical imaging features and a positive CSF tap test is straightforward. However, the difficulty arises when patients do not show characteristic clinical features or do not show a definite improvement to CSF removal. The purpose of diagnostic guidelines in INPH is to identify those patients who are most likely to benefit from shunt surgery. Recently, the American Academy of Neurology has published its own practice guidelines [66]. However, the international [49] and Japanese [62] guidelines are probably the two most widely used and will be given further consideration in this chapter. Both have some similarities but also a few notable differences. The terms ‘possible’ and

Features	International guidelines	Japanese guidelines
Size of ventricles	Ventricular enlargement not entirely attributable to cerebral atrophy or congenital hydrocephalus (Evan's ratio >0.3 or equivalent)	Evan's ratio >0.3
Additional imaging features	No obvious obstruction to CSF flow And at least one of the following: 1. Enlargement of temporal horns not solely due to hippocampal atrophy 2. Callosal angle of 40° or more 3. Evidence of altered brain water content, including periventricular signal changes on CT and MRI not attributable to microvascular ischemic changes or demyelination 4. An aqueductal or fourth ventricular flow void on MRI	Dilated subarachnoid spaces in the Sylvian fissures and narrowed spaces over the high cerebral convexity and medial surface (DESH) One or more elliptically dilated sulci over the medial surface and convexity in isolation* (Figure 2C) A callosal angle of less than 90° on coronal section perpendicular to the anterior commissure-posterior commissure plane*

DESH = disproportionately enlarged subarachnoid space hydrocephalus.

*These features are supportive but not essential for a diagnosis of possible INPH.

Table 1. Imaging features of INPH: comparing the international and Japanese guidelines.

'probable' INPH are employed in each, with diagnostic criteria based on clinical and imaging features. However, the Japanese guidelines use the term 'probable INPH' in those who improve following the removal of CSF. They also label those who respond to shunt surgery as having 'definite' INPH. The international guidelines make no mention of response to CSF removal or shunting in their diagnostic criteria. The neuroimaging criteria also differ. **Table 1** shows a comparison of the diagnostic neuroimaging features used in these guidelines.

8. Predictors of shunt efficacy

Apart from imaging findings and CSF tap test, there are other variables that can influence outcome after shunt surgery. Knowledge of these factors is important, and, when used in conjunction with diagnostic guidelines, can add weight to the decision-making process. Several factors have been associated with either good or poor outcomes. These are summarised in **Table 2**.

The presence of white matter changes is of unclear significance in predicting outcome. The absence of white matter and severe periventricular signals on T2-weighted imaging studies was associated with a good response to shunt placement [71]. The degree of periventricular and deep white matter lesions was shown to be inversely correlated with the degree of clinical improvement in 41 patients [72]. However, as mentioned earlier, Tullberg et al. [51] found that conventional MRI could not reliably differentiate between the causes of white matter changes and that the presence of DWMH or subcortical lacunar infarctions in NPH did not predict a poor outcome from shunt surgery [11]. These patients should not be denied surgery on the basis of these findings alone [11].

Features	Favourable outcome	Poor outcome
Clinical	Gait disturbance occurring before cognitive impairment	Dementia as the initial neurological sign
	Mild or moderate dementia	Severe dementia at presentation
	Shorter duration of symptoms	Dementia for more than 2 years [67, 68]
CSF measures	CSF outflow resistance of 18 mm Hg/ml/min or higher during lumbar constant flow infusion (boon 1998)	
	Occurrence of B-waves during 50% or more of the recording time during continuous ICP monitoring	
Pathological markers		AD pathology on cortical biopsy [69, 70]

Table 2. Factors influencing the outcome of shunt surgery.

9. Shunt surgery

Surgical diversion of CSF via a shunt is the standard intervention for INPH. This is based on the presumption that CSF diversion will reduce or normalise the transmante pressure, thereby stabilising or improving symptoms. Ventriculoperitoneal shunts are most commonly used [73]. It is important to remember that not every patient with possible or probable INPH will be a candidate for shunt surgery. The risk-to-benefit ratio has to be assessed individually. The patient or family should understand that dementia is least likely to improve and that the mean chance of significant improvement is 30–50% [44]. Information about the risks of complications should also be explicit. Initial studies of shunting in INPH reported a low rate of significant long-term improvement, but a high rate of complications [74]. There is no definite consensus on how to best assess response to shunting. Also, there was no randomised control trial comparing the outcomes of shunting until 2011. This was a small study involving 14 patients who were randomised to open or closed shunts [75]. Those who initially had their shunts ligated after surgery had their shunts opened after 3 months. Those with open shunts experienced an improvement in motor and psychometric scores (30 and 23% increase, respectively) at 3 months, whereas those with ligated shunts were unchanged. This group, however, improved following opening of the shunts at 3 months, with an increase in motor and psychometric scores of 28 and 18%, respectively. A systematic review concluded that long-term response was 29% [76]. However, results of more recent studies show a significantly higher rate of 80–90% [2, 77]. It is clear that a general consensus is required to standardise the measurement of outcomes following shunting.

9.1. Complications

In their systematic review, Hebb et al. [76] also found a mean complication rate of 38%. Potential complications include infection, seizures, abdominal problems (peritonitis, perforation, volvulus and ascites), shunt failure or blockage, shunt over-drainage and intracranial haemorrhage. Shunt over-drainage is the commonest complication in the first year occurring in about one-third of patients [76, 78]. Complication rates can differ between centres. The Eu-INPH study revealed a complication rate of 28% [2], while Poca et al. [77] found a complication rate of less than 12% in a prospective study involving 236 patients.

9.2. Follow-up

Follow-up after surgery helps to identify patients who are unchanged or worse, and those who can be helped by further adjustments or shunt revision. Repeat brain imaging is routinely undertaken in the immediate aftermath of surgery, but when performed further down the line, it can also identify a subdural haemorrhage in those who are over-drained. If this is the case, a higher opening pressure should be targeted. Conversely, a retrospective study found that in those with no substantial improvement and in whom under-drainage is suspected, selecting a lower pressure can improve the outcome [79].

10. Conclusions

INPH is probably more common than we realise. Due to its reversibility, it is imperative that not only neurologists but other physicians, in particular geriatricians, are more aware of this condition. Although significant progress has been made in our understanding of this condition, a unifying theory explaining its pathophysiology is still awaited. Numerous pathophysiological changes have been noted, but it remains unclear which is the cause, effect or epiphenomenon. Given that patients with INPH have pathologies such as VD, AD and PSP, among others, we therefore regard INPH as a multi-aetiological disorder. For similar reasons, we feel that the role of neurodegeneration should be explored further. Treatment with shunting remains the gold standard. Unfortunately, too often, the condition eventually progresses.

Author details

Rubesh Gooriah* and Ashok Raman

*Address all correspondence to: rubesh@doctors.org.uk

Department of Neurology, Hull Royal Infirmary, Hull, United Kingdom

References

- [1] Hakim S, Adams RD: The special clinical problem of symptomatic hydrocephalus with normal cerebrospinal fluid pressure. Observations on cerebrospinal fluid hydrodynamics. *J Neurol Sci.* 1965;2:307–27.
- [2] Klinge P, Hellstrom P, Tans J, et al: One-year outcome in the European multicentre study on iNPH. *Acta Neurol Scand.* 2012;126:145–53.
- [3] Tisell M, Hoglund M, Wikkelso C: National and regional incidence of surgery for adult hydrocephalus in Sweden. *Acta Neurol Scand.* 2005;112:72–5.
- [4] Brean A, Eide PK: Prevalence of probable idiopathic normal pressure hydrocephalus in a Norwegian population. *Acta Neurol Scand.* 2008;118:48–53.
- [5] Tanaka N, Yamaguchi S, Ishikawa H, Ishii H, Megura K: Prevalence of possible idiopathic normal-pressure hydrocephalus in Japan: the Osaki-Tajiri project. *Neuroepidemiology* 2009;32:171–5.
- [6] Spetzler RF: Normal pressure hydrocephalus. *Barrow Q.* 2003;19:1.
- [7] Mase M, Yamada K, Banno T, et al: Quantitative analysis of CSF flow dynamics using MRI in normal pressure hydrocephalus. *Acta Neurochir Suppl (Wein).* 1998;71:350–3.

- [8] Bateman G: Vascular compliance in normal pressure hydrocephalus. *Am J Neuroradiol.* 2000;21:1574–85.
- [9] Greitz D, Greitz T, Hindmarsh T: A new view on the CSF-circulation with the potential for pharmacological treatment of childhood hydrocephalus. *Acta Paediatr.* 1997;86:125–32.
- [10] Krauss, JK, Droste DW et al: Cerebrospinal fluid shunting in idiopathic normal-pressure hydrocephalus of the elderly: effect of periventricular and deep white matter lesions. *Neurosurgery* 1996;39(2):292–300.
- [11] Tullberg M, Jensen C, Ekholm S, Wikkelso C: Normal pressure hydrocephalus: vascular white matter changes on MR images must not exclude patients from shunt surgery. *AJNR Am J Neuroradiol.* 2001;22:1665–73.
- [12] Akai K, Uchigasaki S, et al: Normal pressure hydrocephalus. Neuropathological study. *Acta Pathol Jpn.* 1987;37(1):97–110.
- [13] Del Bigio MR: Neuropathological changes caused by hydrocephalus. *Acta Neuropathol.* 1993;85(6):573–85.
- [14] Haubrich C, Czosnyka Z, et al: Is there a direct link between cerebrovascular activity and cerebrospinal fluid pressure-volume compensation? *Stroke.* 2007;38(10):2677–80.
- [15] Grünewald RA: Normal pressure hydrocephalus: pathophysiology. *Pract Neurol.* 2006;6:264–6.
- [16] Castro ME, Portnoy HD, Maesaka J: Elevated cortical venous pressure in hydrocephalus. *Neurosurgery.* 1991;29:232–8.
- [17] Penar PL, Lakin WD, Yu J: Normal pressure hydrocephalus: an analysis of aetiology and response to shunting based on mathematical modelling. *Neurol Res.* 1995;17:83–8.
- [18] Portnoy HD, Branch C, Castro ME: The relationship of intracranial venous pressure to hydrocephalus. *Childs Nerv Syst.* 1994;10:29–35.
- [19] Boon AJ, Tans JT, Delwel EJ, Egeler-Peerdeman SM, Hanlo PW, Wurzer JA, et al: Does CSF outflow resistance predict the response to shunting in patients with normal pressure hydrocephalus? *Acta Neurochir Suppl.* 1998;71:331–3.
- [20] Boon AJ, Tans JT, Delwel EJ, et al: Dutch normal pressure hydrocephalus study: prediction of outcome after shunting by resistance to outflow of cerebrospinal fluid. *J Neurosurg.* 1997;87:687–93.
- [21] Malm J, Kristensen B, Karlsson T, et al: The predictive value of cerebrospinal fluid dynamic tests in patients with the idiopathic adult hydrocephalus syndrome. *Arch Neurol.* 1995;52:783–9.

- [22] Borgesen SE, Gjerris F: The predictive value of conductance to outflow of CSF in normal pressure hydrocephalus. *Brain*. 1982;105:65–86.
- [23] Bradley WG: Normal pressure hydrocephalus: new concepts on etiology and diagnosis. *AJNR Am J Neuroradiol*. 2000;21:1586–90.
- [24] Cabral D, Beach TG, Vedders L, Sue LI, Jacobson S, Myers K, Sabbagh MN: Frequency of Alzheimer's disease pathology at autopsy in patients with clinical normal pressure hydrocephalus. *Alzheimers Dement*. 2011;7(5):509–13.
- [25] Leinonen V, et al: Post-mortem findings in 10 patients with presumed normal-pressure hydrocephalus and review of the literature. *Neuropathol Appl Neurobiol*. 2012;38(1):72–86.
- [26] Kudo T, Mima T, Hashimoto R, Nakao K, Morihara T, et al: Tau protein is a potential biological marker for normal pressure hydrocephalus. *Psychiatry Clin Neurosci*. 2000;54:199–202.
- [27] Tsai A, Malek-Ahmadi M, Kahlon V, Sabbagh NM: Differences in cerebrospinal fluid biomarkers between clinically diagnosed idiopathic normal pressure hydrocephalus and Alzheimer's disease. *J Alzheimers Dis Parkinsonism*. 2014;4(4):1000150.
- [28] Lee PH, Yong SW, Ahn YH, Huh K: Correlation of midbrain diameter and gait disturbance in patients with idiopathic normal pressure hydrocephalus. *J Neurol*. 2005;252:958–63.
- [29] Thompson PD: Frontal lobe ataxia. *Handb Clin Neurol*. 2012;103:619–22.
- [30] Knutsson E, Lying-Tunell U: Gait apraxia in normal pressure hydrocephalus: patterns of movement and muscle activation. *Neurology*. 1985;35:155–60.
- [31] Stolze H, Kuhtz-Buschbeck JP, Drücke H, et al: Comparative analysis of the gait disorder of normal pressure hydrocephalus and Parkinson's disease. *J Neurol Neurosurg Psychiatr*. 2001;70:289.
- [32] Scharre DW: Normal pressure hydrocephalus: measure twice, shunt once. *Neurology* 2011;77:1110–1.
- [33] Gustafson L, Hagberg B: Recovery of hydrocephalic dementia after shunt operation. *J Neurol Neurosurg Psychiatr*. 1978;41:940–7.
- [34] Thomsen AM, Borgesen SE, Bruhn P, et al: Prognosis of dementia in normal pressure hydrocephalus after a shunt operation. *Ann Neurol*. 1986;20:304–10.
- [35] Iddon JL, Pickard JD, Cross JJ, Griffiths PD, Czosnyka M, Sahakian BJ: Specific patterns of cognitive impairment in patients with idiopathic normal pressure hydrocephalus and Alzheimer's disease: a pilot study. *J Neurol Neurosurg Psychiatr*. 1999;67:723–32.

- [36] Ogino A, Kazui H, Miyoshi N, Hashimoto M, Ohkawa S, Tokunaga H, Ikejiri Y, Takeda M: Cognitive impairment in patients with idiopathic normal pressure hydrocephalus. *Dement Geriatr Cogn Disord*. 2006;21:113–9.
- [37] Saito M, Nishio Y, Kanno S, et al: Cognitive profile of idiopathic normal pressure hydrocephalus. *Dement Geriatr Cogn Dis Extra*. 2011;1:202–11.
- [38] Hellström P, Edsbacke M, Archer T, Tisell M, Tullberg M, Wikkelso C: The neuropsychology of patients with clinically diagnosed idiopathic normal pressure hydrocephalus. *Neurosurgery*. 2007;61:1219–26.
- [39] Kazui H: Cognitive impairment in patients with idiopathic normal pressure hydrocephalus. *Brain Nerve*. 2008;60(3):225–31.
- [40] Fisher CM: Hydrocephalus as a cause of disturbances of gait in the elderly. *Neurology* 1982;32:1358–63.
- [41] Bret P, Chazal J: L'hydrocéphalie chronique de l'adulte. *Neurochirurgie*. 1990;36: [Suppl]1–159.
- [42] Sakakibara R, Kanda T, Sekido T, et al: Mechanism of bladder dysfunction in idiopathic normal pressure hydrocephalus. *Neurourol Urodyn*. 2008;27:507–10.
- [43] Sakakibara R, Uchiyama T, Kanda T, Uchida Y, Kishi M, Hattori T: Urinary dysfunction in idiopathic normal pressure hydrocephalus. *Brain Nerve*. 2008;3:233–9.
- [44] Vanneste JA: Diagnosis and management of normal-pressure hydrocephalus. *J Neurol*. 2000;247:5–14.
- [45] Williams MA, Relkin NR: Diagnosis and management of idiopathic normal-pressure hydrocephalus. *Neurol Clin Pract*. 2013;3:375–85.
- [46] Toma AK, Holl E, Kitchen ND et al: Evans' index revisited: the need for an alternative in normal pressure hydrocephalus. *Neurosurgery*. 2011;68 (4):939–44.
- [47] Benson DF, LeMay M, Patten DH, Rubens AB: Diagnosis of normal-pressure hydrocephalus. *N Engl J Med*. 1970;283:609–15.
- [48] Sjaastad O, Nordvik A: The corpus callosal angle in the diagnosis of cerebral ventricular enlargement. *Acta Neurol Scand*. 1973;49:396–406.
- [49] Relkin N, Marmarou A, Klinge P, et al: Diagnosing idiopathic normal-pressure hydrocephalus. *Neurosurgery*. 2005;57(3):S4–16.
- [50] Ishii K, Soma T, Shimada K, Oda H, Terashima A, Kawasaki R: Automatic volumetry of the cerebrospinal fluid space in idiopathic normal pressure hydrocephalus. *Dement Geriatr Cogn Dis Extra*. 2013;3(1):489–96.
- [51] Tullberg M, Hultin L, Ekholm S, Mansson JE, Fredman P, Wikkelso C: White matter changes in normal pressure hydrocephalus and Binswanger disease: specificity,

- predictive value and correlations to axonal degeneration and demyelination. *Acta Neurol Scand.* 2002;105:417–26.
- [52] Di Rocco C, Di Trapani G, Maira G, Bentivoglio M, Macchi G, Rossi GF: Anatomico-clinical correlations in normotensive hydrocephalus. Reports on three cases. *J Neurol Sci.* 1977;33:437–52.
- [53] Sherman JL, Citrin CM, Gangarosa RE, Bowen BJ: The MR appearance of CSF flow in patients with ventriculomegaly. *AJNR Am J Neuroradiol.* 1986;7:1025–31.
- [54] Bradley WG, Kortman KE, Burgoyne B: Flowing cerebrospinal fluid in normal and hydrocephalic states: appearance on MR images. *Radiology.* 1986;159:611–6.
- [55] Bradley WG Jr, Whittemore AR, Kortman KE, et al: Marked cerebrospinal fluid void: indicator of successful shunt in patients with suspected normal-pressure hydrocephalus. *Radiology.* 1991;178:459–66.
- [56] Krauss JK, Regel JP, Vach W, Jungling FD, Droste DW, Wakhloo AK: Flow void of cerebrospinal fluid in idiopathic normal pressure hydrocephalus of the elderly: can it predict outcome after shunting? *Neurosurgery* 1997;40:67–73.
- [57] Gideon P, Stahlberg F, Thomsen C, Gjerris F, Sørensen PS, Henriksen O: Cerebrospinal fluid flow and production in patients with normal pressure hydrocephalus studied by MRI. *Neuroradiology.* 1994;36:210–5.
- [58] Bradley WG Jr, Scalzo D, Queralt J, Nitz WN, Atkinson DJ, Wong P: Normal-pressure hydrocephalus: evaluation with cerebrospinal fluid flow measurements at MR imaging. *Radiology.* 1996;198:523–9.
- [59] Hakim R, Black PM: Correlation between lumboventricular perfusion and MRI-CSF flow studies in idiopathic normal pressure hydrocephalus. *Surg Neurol.* 1998;49:14–19.
- [60] Wikkelsø C, Hellström P, Klinge PM, Tans JT; European iNPH Multicentre Study Group: The European iNPH Multicentre Study on the predictive values of resistance to CSF outflow and the CSF Tap Test in patients with idiopathic normal pressure hydrocephalus. *J Neurol Neurosurg Psychiatr.* 2013;84:562–8.
- [61] Ishikawa M, Hashimoto M, Kuwana N, Mori E, Miyae H, Wachi A, et al: Guidelines for management of idiopathic normal pressure hydrocephalus. *Neurol Med Chir (Tokyo).* 2008;48:S1–23.
- [62] Mori E, Ishikawa M, Kato T, et al: Japanese Society of Normal Pressure Hydrocephalus. Guidelines for management of idiopathic normal pressure hydrocephalus: second edition. *Neurol Med Chir (Tokyo).* 2012;52:775–809.
- [63] Yamada S, Ishikawa M, Miyajima M, Atsuchi M, Kimura T, Kazui H, Mori E: Disease duration: the key to accurate CSF tap test in iNPH. *Acta Neurol Scand.* 2016. doi: 10.1111/ane.12580

- [64] Walchenbach R, Geiger E, Thomeer RT, et al: The value of temporary external lumbar CSF drainage in predicting the outcome of shunting on normal pressure hydrocephalus. *J Neurol Neurosurg Psychiatr.* 2002;72:503–6.
- [65] Woodworth GF, McGirt MJ, Williams MA, Rigamonti D: Cerebrospinal fluid drainage and dynamics in the diagnosis of normal pressure hydrocephalus. *Neurosurgery* 2009;64:919–25.
- [66] Halperin JJ, Kurlan R, Schwalb JM, Cusimano MD, Gronseth G, Gloss D: Practice guideline: idiopathic normal pressure hydrocephalus: response to shunting and predictors of response: report of the guideline development, dissemination, and implementation subcommittee of the American academy of neurology. *Neurology.* 2015;85:2063–71.
- [67] Petersen RC, Mokri B, Laws ER Jr: Surgical treatment of idiopathic hydrocephalus in elderly patients. *Neurology.* 1985;35(3):307.
- [68] Marmarou A, Young HF, Aygok GA, Sawauchi S, Tsuji O, Yamamoto T, Dunbar J: Diagnosis and management of idiopathic normal-pressure hydrocephalus: a prospective study in 151 patients. *J Neurosurg.* 2005;102(6):987.
- [69] Hamilton R, Patel S, Lee EB, Jackson EM, Lopinto J, Arnold SE, Clark CM, Basil A, Shaw LM, Xie SX, Grady MS, Trojanowski JQ: Lack of shunt response in suspected idiopathic normal pressure hydrocephalus with Alzheimer disease pathology. *Ann Neurol.* 2010;68(4):535.
- [70] Savolainen S, Hurskainen H, Paljarvi L, Alafuzoff I, Vapalahti M: Five year outcome of normal pressure hydrocephalus with or without a shunt: predictive value of the clinical signs, neuropsychological evaluation and infusion test. *Acta Neurochir.* 2002;144:515–23.
- [71] Jack CR Jr, Mokri B, Laws ER Jr, Houser OW, Baker HL Jr, Petersen RC: MR findings in normal-pressure hydrocephalus: significance and comparison with other forms of dementia. *J Comput Assist Tomogr.* 1987;11:923–31.
- [72] Krauss JK, Droste DW, Vach W, Regel JP, Orszagh M, Borremans JJ, Tietz A, Seeger W: Cerebrospinal fluid shunting in idiopathic normal-pressure hydrocephalus of the elderly: effect of periventricular and deep white matter lesions. *Neurosurgery* 1996;39:292–9.
- [73] Bergsneider M, Black PM, Klinge P, Marmarou A, Relkin N: Surgical management of idiopathic normal-pressure hydrocephalus. *Neurosurgery* 2005;57(3 suppl):S29–39.
- [74] Stein SC, Burnett MG, Sonnad SS: Shunts in normal-pressure hydrocephalus: do we place too many or too few? *J Neurosurg.* 2006;105:815–22.
- [75] Tisell M, Tullberg M, Hellstrom P, Edsbacke M, Hogfeldt M, Wikkelso C: Shunt surgery in patients with hydrocephalus and white matter changes. *J Neurosurg.* 2011;114:1432–8.

- [76] Hebb AO, Cusimano MD: Idiopathic normal pressure hydrocephalus: a systematic review of diagnosis and outcome. *Neurosurgery*. 2001;49(5):1166.
- [77] Poca MA, Solana E, et al: Idiopathic normal pressure: results of a prospective cohort of 236 shunted patients. *Acta Neurochir*. 2012;114:247–53.
- [78] Khan QU, Wharen RE, Grewal SS, Thomas CS, Deen HG Jr, Reimer R, Van Gerpen JA, Crook JE, Graff-Radford NR: Overdrainage shunt complications in idiopathic normal-pressure hydrocephalus and lumbar puncture opening pressure. *J Neurosurg*. 2013;119(6):1498–502.
- [79] Zemack G, Romner B: Adjustable valves in normal-pressure hydrocephalus: a retrospective study of 218 patients. *Neurosurgery*. 2002;51(6):1392–400.