Movement Disorders
CLINICAL PRACTICE
REVIEW

A Review of Clinical Outcomes for Gait and Other Variables in the Surgical Treatment of Idiopathic Normal Pressure Hydrocephalus

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Abstract: Background: Idiopathic normal pressure hydrocephalus (INPH) is a treatable cause of gait disturbance, cognitive impairment, and urinary incontinence. This clinical triad of symptoms occurs in association with ventriculomegaly and normal cerebrospinal fluid (CSF) pressure. Although the treatment outcomes after CSF shunting for INPH have improved significantly since its first description in 1965, shortcomings in our understanding still remain. Not all INPH patients exhibit clinical improvement after shunting, and it is challenging to identify patients who are more likely to benefit from shunting.
Methods: The Cochrane Library, Medline, Embase, and PubMed databases were searched for English-language publications between 1965 and October 2015. Reference lists of publications were also manually searched for additional publications.
Results: The findings of this review indicate that, despite efforts to improve patient selection, the degree of clinical improvement after shunting continues to demonstrate significant variability both within and between studies. These discrepancies in treatment outcomes are the result of controversies in 3 distinct but interrelated domains: the underlying pathophysiology of INPH, the diagnosis of INPH, and the identification of likely shunt-responders.
Conclusions: This review focuses on these 3 areas and their relation to surgical treatment outcomes. Despite the limitations of published outcome studies and limitations in our understanding of INPH pathophysiology, shunting is a safe and effective means of achieving meaningful clinical improvement in most patients with INPH.

Normal pressure hydrocephalus (NPH) was first reported in 1965 as a triad of dementia, gait disturbance, and urinary incontinence, with associated ventricular dilatation and normal cerebrospinal fluid (CSF) pressure.[1] NPH can be classified as idiopathic NPH (INPH) or secondary NPH (SNPH), the latter of which occurs most commonly after subarachnoid hemorrhage, trauma, or meningitis.[2] Although CSF diversion via a shunt is the mainstay of NPH management, surgical outcomes in INPH have been consistently less successful than those in SNPH.[3–5] In addition, the reported rates of postoperative clinical improvement in INPH patients have varied from 24% to 96%.[6,7] These discrepancies in treatment outcomes are the result of controversies in 3 domains: the underlying pathophysiology of INPH, the diagnosis of INPH, and the identification of likely shunt-responders.

This review focuses on these 3 areas of controversy and their relation to surgical outcomes. The Cochrane Library, Medline, Embase, and PubMed were searched for English-language publications between 1965 and October 2015 using a combination of medical subject headings and free text key words such as: "normal pressure hydrocephalus," "treatment," "outcome," and "cerebrospinal fluid shunt." Reference lists of publications

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were also manually searched for additional publications relevant to the scope of this review.

Epidemiology

Both SNPH and INPH occur in approximately equal proportions.[8] However, SNPH can occur at any age, whereas INPH typically occurs during the seventh decade of life. Furthermore, there has been no identifiable association between NPH and either sex or any ethnicity.[9,10] Studies have estimated that the incidence of NPH is from 0.84 to 5.5 per 100,000[11,12] and that the prevalence is from 0.41% to 1.4% for persons aged 65 years or older.[13,14] However, most epidemiological studies are hospital-based, and community-based epidemiological data are lacking.[12] One retrospective study of 4 nursing homes found that the incidence of NPH was between 9% and 14%.[15] These variations clearly reflect difficulties in the definition and identification of NPH.[2,8]

Pathophysiology

To date, no clear pathophysiological mechanism for INPH has been established.[2] Earlier hypotheses suggested the possibility of defective CSF absorption secondary to leptomeningeal fibrosis,[4,16] but several studies have demonstrated no significant association between leptomeningeal fibrosis and the CSF outflow resistance or clinical outcomes.[16,17] Other early studies identified a transmantle pressure gradient from the ventricular wall to the cortical surface as a factor in the development of ventriculomegaly in both experimental models and patients with NPH.[18,19] However, in another experimental model, Shapiro et al.[20] subsequently demonstrated that ventricular expansion can also progress even in the absence of a measurable transmantle pressure gradient, suggesting that such a gradient is unlikely to solely account for the pathological findings of INPH.

CFS Mechanisms

Because CSF diversion can improve INPH symptoms, it is likely that a dysfunction of the CSF circulation is involved. Animal and hydrodynamic human studies have implicated elevations of CSF pressure as a core defect in INPH.[21,22] The increased frequency of episodic pressure elevations, called B-waves, observed on continuous intracranial pressure (ICP) monitoring is consistent with this.[23] It is generally accepted that this increased ICP pulse amplitude suggests a decrease in brain compliance, which may play a central role in INPH pathophysiology.[24] Previous canine studies have demonstrated that brain compliance is dynamic and displays a frequency-dependent function with enhanced pulsatility absorbance around cardiac frequency.[25] This phenomenon is diminished in canine models of hydrocephalus as well as in INPH patients.[23,26] In keeping with these experimental findings, Eide and Sorteberg[24] demonstrated that 93% of patients with increased ICP pulsatility improved after shunt surgery compared with only 10% of patients without increased ICP pulsatility. The failure of a pulsation absorber mechanism among INPH patients—and relative normalization of this mechanism after shunt surgery—may explain why higher amplitude ICP waves were seen more frequently in INPH patients who improved after shunt surgery.[24] However, Czosnyka et al.[27] also found no evidence suggesting that an increased pulse amplitude was a factor in promoting ventricular dilatation and highlighted the need to consider these findings in the context of other clinical and CSF compensation parameters. In any case, there is now common agreement that CSF pressures are not always "normal" in INPH, and some have even adopted the term "idiopathic adult hydrocephalus syndrome."[28]

Cerebrovascular Mechanisms

Interestingly, Meier and Mutze[29] demonstrated that a favorable response to shunting is not predicated by a reduction in ventriculomegaly. In fact, greater clinical benefit was seen in patients with minimal postoperative ventricular size change, suggesting that CSF dynamics alone cannot explain all the features of INPH. To this effect, many authors have suggested a cerebrovascular component to INPH pathophysiology due to its strong association with vascular risk factors such as hypertension.[2] Hypertension causes arterial wall thickening and arteriosclerosis, which predispose patients to microinfarcts in vessels such as the lenticulostriate arteries that have a long course through the brain parenchyma.[30] This is supported by Akai et al.,[31] who found arteriosclerosis, demyelination, organized thrombi, and microinfarcts in the deep and periventricular white matter of NPH patients. Other studies have also alluded to associations between INPH, deep white matter ischemia, and even Binswanger's disease—which some have suggested may in fact represent the same pathophysiological process.[32,33] In light of such findings, several authors have hypothesized that these vascular phenomena impair brain viscoelasticity and permit ventricular enlargement with relatively normal CSF pressures.[32,34]

Conversely, it is possible that ventricular enlargement increases interstitial pressure, secondarily impairing periventricular blood flow and resulting in ependymal disruption, microinfarctions, gliosis, and neuronal degeneration.[31,35] Using a canine model of chronic hydrocephalus, Luciano et al.[36] demonstrated dynamic changes in capillary vessel diameter and density that may reflect adaptive processes occurring to maintain adequate cerebral perfusion in chronic hydrocephalus. Although the exact mechanism behind these adaptive changes is unclear, vascular endothelial growth factor (VEGF) appears to be involved. Increased levels of VEGF can be detected in the CSF of both chronic hydrocephalus canines and humans alike, possibly reflecting a hypoxic response.[37,38] Furthermore, higher levels of VEGF are found in patients who have no improvement after CSF drainage, suggesting that a greater ischemic injury burden may be responsible for the poor treatment response in these patients.[37]

Vascular injury in INPH patients may also result in a subsequent reduction in CSF turnover that impairs the clearance of neurotoxic metabolites such as β-amyloid, tau-protein, and

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proinflammatory cytokines.[39] Because INPH frequently occurs in combination with both Alzheimer's and cerebrovascular disease, such mechanisms that can causally relate these 3 entities are attractive.[31,40] One such hypothesis proposes that INPH is caused by the loss of vascular and CSF pulsation dampening, or the Windkessel effect.[41] In this model, impaired vascular compliance causes elevated venous pressures, which can account for ventricular enlargement, cerebral hypoperfusion, and thus a diminished CSF turnover.[42]

Some authors have also proposed the possibility of a protracted early-onset mechanism whereby INPH is the end result of a "2-hit" process: benign external hydrocephalus (BEH) in infancy with subsequent deep white matter ischemia (DWMI) in late adulthood.[43] BEH is believed to be the result of a mismatch in CSF production and absorption by immature arachnoid vili.[44] This results in a relative increase in head circumference that persists in adulthood—a finding that Bradley et al.[45] demonstrated when comparing the intracranial volumes of INPH patients with those of age-matched and sex-matched controls. It is hypothesized that these BEH individuals are at least partially dependent on CSF egress to the subarachnoid space via an extracellular route. DWMI may impair this extracellular route of CSF flow and cause increasing resistance, ventriculomegaly, and INPH symptoms.[43] In keeping with this hypothesis, Bradley et al.[43] demonstrated significantly higher apparent diffusion coefficients in NPH patients compared with controls, suggesting increased fluid content in the extracellular space of NPH patients.

Diagnosis

Diagnosing INPH is difficult, and the accepted gold standard for diagnosis is clinical improvement after shunt surgery.[2] This implies a circular argument: shunt-responsive INPH (SR-INPH) is defined by a clinical response to CSF diversion. Given that there are patients with an identical clinical picture and no clinical improvement after CSF diversion, it is reasonable to assume that INPH is a broader clinical syndrome with shunt-responsive and nonresponse subgroups. Therefore, ancillary investigations, such as trial CSF drainage tests, may be considered as supplementary prognostic[46] tests rather than diagnostic tests, predicting shunt responsiveness rather than defining the INPH syndrome. As a result, there is no definitive clinical or diagnostic test for INPH. This has left room for some clinicians to question whether the syndrome actually exists, arguing that it is rare at best.[47]

Nevertheless, Relkin et al.[48] stipulate that diagnosing INPH only involves the clinical history and examination, neuroimaging, and CSF opening pressure. Because different degrees of diagnostic certainty can follow these routine assessments, some authors have also proposed classifying INPH as "probable," "possible," or "unlikely."[48,49] However, the use of these terms varies across different contexts and is often without explicit definition, making interpretation of the literature difficult. Herein, we define INPH as a presumed clinical syndrome in its broadest sense, regardless of its treatment response.

Clinical History and Examination

Reported symptoms should demonstrate an insidious onset after age 40 years and progress over at least 3 to 6 months.[48] There should also be no alternative medical explanation of the symptoms or any antecedent events indicating secondary NPH.

Gait disturbance is usually the first symptom and the most responsive to shunting.[50] The "classical" gait of INPH is characterized by a slow, short-stepped shuffling with a slightly broad base, reduced step-height, and associated gait freezing.[51] Arm swing may be relatively preserved when considering stride length and gait speed; occasionally, arm swing is noticeably increased. It may also include postural instability and difficulty turning.[48,50] These gait disturbances are consistent with subcortical deficits involving the basal ganglia and frontal periventricular pathways.[52,53] Using diffusion tensor imaging (DTI), Lenfeldt et al.[54] provided further support for hypothesis by demonstrating axonal loss in anterior frontal white matter tracts that are involved in movement planning.

Although Adams et al.[1] originally reported INPH as a reversible dementia, dementia is in fact the triad symptom least likely to improve postoperatively.[9,55] The typical cognitive deficits of INPH are "subcortical," with psychomotor retardation, apathy, difficulty in executive functions, and impaired recall memory yet relatively preserved recognition memory.[56] Although the underlying pathophysiology of these deficits is unclear, the frontostriatal system and periventricular projections have again been implicated.[53]

Urinary symptoms in INPH usually begin as increased frequency and urgency, only developing into incontinence in later stages.[57] Urinary symptoms respond well to shunting but only predict a functional improvement in 31% to 33% of patients.[7,58] Although incontinence may also occur secondary to gait disturbance or dementia, detrusor over activity is believed to be the primary mechanism, and this is consistent with frontal and basal ganglia dysfunction.[59]

Despite classically being a triad of symptoms, INPH can be diagnosed in the presence of gait disturbance and 1 other cardinal symptom.[48] This is in light of findings revealing that the complete triad often represents prolonged symptom duration, more advanced disease, and a poorer prognosis.[60]

Neuroimaging

Neuroimaging evidence of hydrocephalus on computerized tomography (CT) or magnetic resonance imaging (MRI) is essential for the diagnosis of INPH. This requires demonstrating ventricular dilatation out of proportion to cerebral atrophy and an absence of macroscopic obstruction to CSF flow.[48] The degree of ventriculomegaly is commonly quantified by the Evans ratio, which is calculated as a ratio of the maximum frontal horn diameter to the maximal biparietal diameter between the inner tables of the skull (Fig. 1).[61] An Evans ratio greater than 0.3 is generally regarded as sufficient confirmation of ventriculomegaly for INPH diagnosis.[48] Other complex methods for quantifying ventriculomegaly in INPH have also been described but are yet to be sufficiently validated or widely

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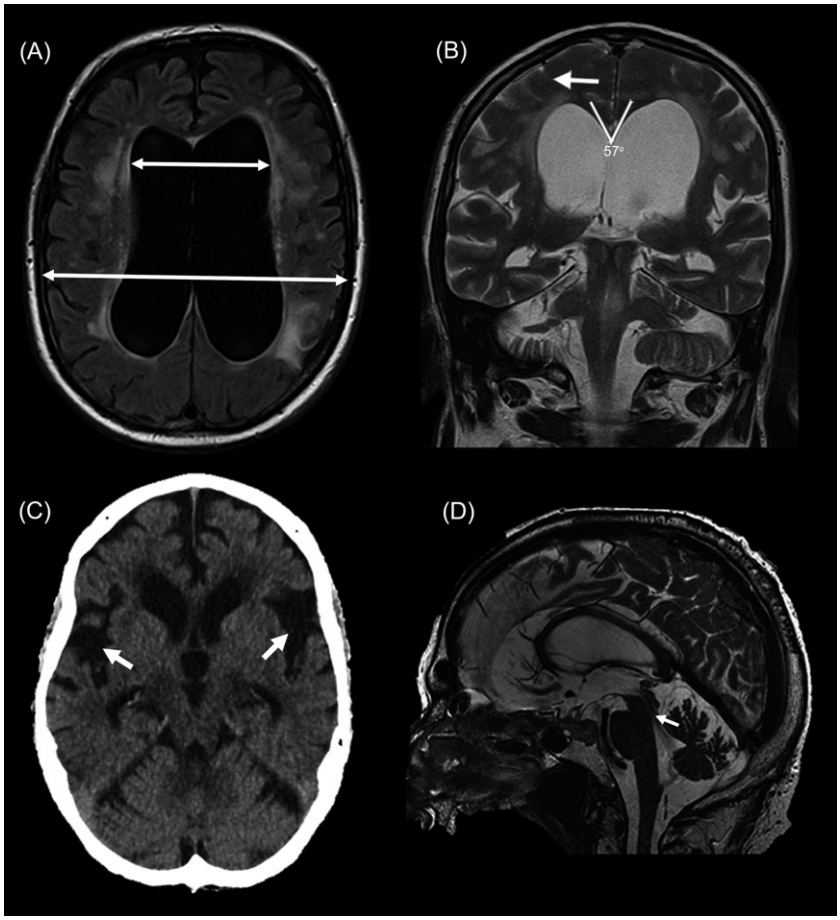

Figure 1 A series of magnetic resonance imaging (MRI) features are consistent with a diagnosis of idiopathic normal pressure hydrocephalus (INPH). (A) Disproportionate ventriculomegaly with an Evans ratio of 0.44 was measured by the ratio of the maximum frontal horn diameter to the maximal biparietal diameter (white arrows). (B) An acute callosal angle (labeled) and "tight" convexity with narrow cerebrospinal fluid spaces (white arrow) are shown. (C) Disproportionate enlargement of the Sylvian fissures (bilateral white arrows) is observed. (D) A T2-weighted MRI demonstrates an aqueductal flow void (white arrow).

adopted.[62] Newer MRI techniques like DTI have also emerged.[63] DTI allows for the quantitative assessment of the magnitude and 3-dimensional direction of water diffusion along white matter tracts of interest.[64] Through measurements of mean diffusivity and fractional anisotropy in regions of interest, such as the corpus callosum, internal capsule, hippocampus, and frontal subcortical and periventricular white matter, a number of studies have demonstrated differences between patients with INPH, Parkinson's disease, and Alzheimer's disease that may assist diagnosis.[65–67] Although promising, novel imaging modalities like DTI or others that assess CSF hydrodynamics, metabolism, or blood flow do not currently have sufficient large-scale studies to support an established diagnostic role.[48]

CFS Opening Pressure

The traditional concept of "normal" CSF opening pressure as a defining feature of INPH has been criticized.[68] Nevertheless, an opening pressure outside the range of 70 to 245 mm H_2O is not consistent with the diagnosis of INPH, and it is still recommended that CSF opening pressure be measured at the time of lumbar puncture or other investigations.[48]

Differential Diagnosis

Much of the diagnostic uncertainty surrounding INPH relates to difficulties distinguishing INPH from other diagnoses common in the elderly.[8] In 1 study of 71 patients referred to a memory clinic with suspected INPH, only 20% had INPH as their final diagnosis.[69] Therefore, differentiating between INPH and other subcortical dementias is essential—particularly Binswanger's disease, subcortical arteriosclerotic encephalopathy, and multi-infarct dementia, which can also present with similar symptoms.[70,71] Fortunately, unlike INPH, gait disturbances in these diseases generally occur in advanced stages, and extensive leukoaraiosis on CT/MRI is more common in vascular

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dementias.[72] Parkinson's disease and other extrapyramidal syndromes, such as progressive supranuclear palsy, may also combine gait disturbance, subcortical cognitive deficits, and urinary symptoms.[8] Differentiating INPH from classical Alzheimer's disease is less difficult, as the cortical pattern of dementia in Alzheimer's disease predominates over other symptoms, and the presence of hippocampal atrophy on CT/MRI may also assist its confirmation.[73,74] When the NPH triad is incomplete, it is especially important to differentiate INPH from other causes of gait/balance disturbance, cognitive deficits, and urinary symptoms (see Table 1). It is also important to note that multiple comorbidities are common in the elderly and can mimic INPH, particularly when there is neuroimaging evidence of mild hydrocephalus. Examples of this include polypharmacy (especially anticholinergic, antiepileptic, or antipsychotic medications), chronic alcoholism with prostatism, or dementia with Lewy bodies and uterine prolapse.

Prognostic Investigations

When a diagnosis of probable INPH is established on clinical and radiological grounds, the positive predictive value for a shunt response may be as low as 58%.[49] Hence, even with a correct clinical diagnosis of INPH, an unfavorable shunt outcome can still occur. This implies either a highly inaccurate diagnosis or an accurate diagnosis but only partially effective therapy; or, perhaps more likely, a combination of both. It is therefore important to identify SR-INPH through further assessment.[46]

TABLE 1 Conditions to consider in the differential diagnosis of idiopathic normal pressure hydrocephalus*

Neurodegenerative disorders	**Other hydrocephalus disorders**
Alzheimer's disease	Aqueduct stenosis
Parkinson's disease	Arrested hydrocephalus
Dementia with Lewy bodies	Long-standing overt ventriculomegaly of adults (LOVA)
Frontotemporal dementia	Non-communicating hydrocephalus
Corticobasal degeneration	Secondary normal pressure hydrocephalus
Progressive supranuclear palsy	**Miscellaneous**
Multiple system atrophy	B12 deficiency
Spongiform encephalopathy	Traumatic brain injury
Vascular	Spinal stenosis
Cerebrovascular disease	Chiari malformation
Vertebrobasilar insufficiency	Wernicke's encephalopathy
Infectious diseases	Carcinomatous meningitis
Human immunodeficiency virus	Spinal cord tumor
Syphilis	Orthostatic myoclonus
Urological disorders	Drug-induced parkinsonism
Bladder or prostate cancer	Anxiety, depression, fear of falling
Benign prostatic hypertrophy	Functional (psychogenic)
Medications (e.g. anticholinergic)	

*Adapted from Klassen and Ahlskog[47], Relkin et al.[48] and Bech-Azeddine et al.[69]

Radionuclide Cisternography

Radionuclide cisternography was originally used to identify SR-INPH by demonstrating ventricular reflux and stagnation over the convexities.[75] However, Vanneste et al.[76] revealed that cisternography was worse than combined clinical and CT criteria at identifying SR-INPH in 33% of cases. Black[58] also found that 55% of INPH patients with normal cisternography were actually shunt-responsive. More recently, the use of CT cisternography has also been investigated; however, this has also been unsuccessful in improving predictive accuracy.[77]

Infusion Studies

CSF infusion studies aim to assess CSF absorptive capacity by measuring the outflow resistance (R_{out}) or its inverse: conductance.[78] Despite employing different infusion and pressure-measuring techniques, studies have consistently demonstrated a positive predictive value over 80%.[79,80] However, the overall predictive accuracy in most studies has been diminished by a poor negative predictive value as low as 27% to 31%.[28,79] Whereas the predictive uncertainty may be related to the heterogeneity of infusion methods and differing threshold values of R_{out} adopted across studies,[48] it may also reflect our incomplete understanding of INPH pathophysiology. Because INPH is likely to involve more complex changes than those seen in CSF dynamics alone, infusion studies may represent an incomplete assessment of INPH. Consequently, it is not surprising that prospective selection of SR-INPH is difficult using infusion studies alone.

CSF Drainage Tests

The drainage of 30 to 50 mL of CSF through a "tap test" is believed to simulate shunting and may produce transient clinical improvements that predict SR-INPH.[5] Studies have demonstrated positive predictive values as high as 94% to 100%[80,81]; however, numerous studies have also found negative predictive values of only 23% to 32%.[28,82] In addition, Kahlon et al.[80] found that 58% of SR-INPH patients would have been overlooked for shunting if the CSF tap test was used in isolation. As a result, patients with INPH can be selected for shunting based on a positive CSF tap test but cannot be excluded based on a negative CSF tap test.[48]

External lumbar drainage (ELD) attempts to reduce the high false-negative rate observed with the CSF tap test by draining more CSF over a number of days in-hospital.[83] Earlier small-sample studies used 5-day to 6-day draining protocols and were able to achieve 100% sensitivity and specificity.[81,84] Unfortunately, larger, more recent studies have still found that the negative predictive value of ELD varies from 36% to 78%.[60,82] Nevertheless, most ELD studies have demonstrated less false-

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negatives and greater predictive accuracy than the CSF tap test.[60,81,85,86] The added cost and morbidity of ELD from hospitalization and potential complications such as meningitis caution against the routine use of this technique.[2,87]

ICP Monitoring

The use of ICP monitoring is controversial.[46] Whereas earlier NPH studies found that B-wave activity occurring greater than 50% of recording time was correlated with shunt response,[4,22] others have debated this.[86] Alternatively, Raftopoulos et al.[88] proposed that specific B-wave morphologies were correlated with shunt response. More recently, other authors have also found that the mean ICP wave amplitude is significantly higher in patients with SR-INPH,[24,27] and Eide and Brean[89] achieved a 91% clinical response rate in those with elevated ICP wave amplitudes. However, ICP monitoring is not always abnormal in INPH, and few studies have confirmed these findings. Consequently, the predictive role of ICP monitoring is not completely understood.

Adjunctive Neuroimaging

Although CT is an adequate imaging modality to establish ventriculomegaly, MRI more readily permits the evaluation of additional features that correlate positively with INPH.[2] A prominent MRI flow void in the cerebral aqueduct is indicative of an increased flow velocity and was thought to be predictive of SR-INPH (Fig. 1).[90] However, others have described no difference in flow void occurrence between INPH patients and normal individiualss[91] and have reported that successful shunting does not necessarily alter flow void signals.[92] CSF stroke volumes above 42 μL on phase-contrast MRI have also been associated with shunt response.[92] Whereas some studies have supported this promising result,[93] others have not.[94]

An acute callosal angle[95] and a "tight" high convexity with narrowed CSF spaces[96] (Fig. 1) have also been identified as predictors of SR-INPH. Kitagaki et al.[96] further described disproportionate enlargement of the Sylvian fissures, basal cisterns, and focal sulci as features supporting a diagnosis of SR-INPH (Fig. 1). Given the lack of a pressure gradient between the ventricles and subarachnoid spaces in INPH,[97] it is postulated that CSF may accumulate in either space—causing so-called "disproportionately enlarged subarachnoid-space hydrocephalus" (DESH).[98] This phenomenon may be difficult to distinguish from focal cortical atrophy and has not been widely investigated internationally. Nevertheless, Japanese diagnostic criteria for INPH include the presence of DESH and further subdivide INPH into DESH and non-DESH forms.[2]

Aside from its potential diagnostic role, DTI has also been investigated as a potential prognostic and follow-up utility. Using DTI, Jurcoane et al.[99] demonstrated increased fractional anisotropy and axial diffusivity in the corticospinal tracts of SR-INPH patients compared with nonresponders. Scheel et al.[100] also examined these DTI parameters before and after shunt surgery and demonstrated a trend toward normalization postoperatively, further suggesting a potential follow-up role for DTI imaging.

Alternative imaging modalities for cerebral blood flow and measurements of CSF biomarkers have also been investigated. However, their predictive value for SR-INPH is still unknown.[99,101–104]

Surgical Treatment

The mainstay of treatment for INPH involves CSF diversion through a shunt. Numerous shunt types, including ventriculoatrial, ventriculopleural, lumboperitoneal, and ventriculoperitoneal (VP) shunts, have been used.[105] Although differences in outcomes between shunt configurations have not been proven,[106] VP shunts are commonly used.

The valves that these shunts use can be flow-regulated or differential pressure-regulated. It is unclear which mechanism produces better outcomes, and Weiner et al.[107] found no difference in clinical outcomes or shunt survival. Furthermore, Boon et al.[108] compared different valve pressure settings and found no statistically significant association with shunting outcome. Programmable valves have now been adopted, as they permit noninvasive pressure adjustments that can optimize clinical improvement and ameliorate drainage-related complications.[105] There is a lack of evidence comparing clinical outcomes between programmable and nonprogrammable valves. However, the reported rates of infection and shunt occlusion appear comparable,[83] so programmable valves are being used more frequently.

Overall, shunt-related complications occur in up to 38% of patients, 22% require additional surgery, and there is a 6% rate of permanent neurological deficit or death.[83] Common complications include shunt malfunctions, infections, headaches, and drainage-related subdural hematomas or effusions.[2] Interestingly, some authors have debated whether shunt-related complications produce any long-term detrimental effects at all.[108,109] Given the frailty of most study populations, studies with longer follow-up periods also face difficulties differentiating between shunt-related complications and other age-related or comorbidity-related complications.[83] It is important to note that general surgical complications may also occur, including deep vein thrombosis, pulmonary embolism, and myocardial infarction. Postoperative delirium is also common.

Endoscopic third ventriculostomy (ETV) has also been proposed by some authors as an alternative treatment to VP shunting. Using ETV in a cohort of 110 patients with INPH, Gangemi et al.[110] achieved a 69.1% improvement rate and a 6.4% complication rate. Although some authors have demonstrated similar promising results with ETV,[111] a randomized clinical trial by Pinto et al.[112] suggested VP shunting as the superior surgical treatment, with better outcomes 12 months postoperatively. Furthermore, Chan et al.[113] also demonstrated an inferior short-term safety profile for ETV compared with VP shunting. As such, the role of ETV in INPH remains unclear without further prospective, randomized studies.

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Clinical Outcomes

Given the lack of clinical equipoise regarding efficacy, randomized control trials comparing CSF diversion with placebo or active nonsurgical treatment have not been widely conducted.[114] However, the SINPHONI-2 (Study of INPH on Neurological Improvement) open-label, randomized trial compared the outcomes between lumboperitoneal shunt surgery within 1 month (immediate treatment group) and surgery postponed for 3 months (postponed treatment group). In their cohort of 93 patients with INPH, 65% of the immediate surgery group demonstrated an improvement in modified Rankin scale of at least 1 point at 3 months compared with 5% in the postponed treatment group.[115] Their results not only demonstrate a benefit for CSF diversion but suggest a need for further studies to investigate whether lumboperitoneal shunt surgery should be considered first-line treatment. Nonrandomized studies have also demonstrated significant clinical benefits from shunting. A systematic review of 64 outcome studies demonstrated that 71% (range, 28%–100%) of patients with INPH had a positive outcome at 1 year after shunt insertion and that 65% (range, 31%–96%) demonstrated improvement beyond 3 years.[116]

Although there are significant discrepancies in these reported rates of clinical improvement, some degree of this variability is likely historical. Early studies reported improvement rates of 24% to 33%,[3,117,118] with the low response rate perhaps in part due to the inclusion of patients with predominating dementia or dementia alone—a poor prognostic indicator.[109] In contrast, 30 studies published since 2006 that were included in the systematic review by Toma et al.[116] demonstrated an overall improvement rate of 82% at 1 year and 73% at 3 years or beyond. Although the selection of appropriate surgical candidates appears to have improved, some studies remain pessimistic. One recent community-based study reported that misdiagnosis was common, true INPH was rare, and only one-third of patients maintained improvement, whereas up to one-third experienced shunt surgery complications.[47]

The marked differences in outcomes between studies may also reflect the variable inclusion of patients with poor-outcome risk factors. These include the presence of the full triad of INPH symptoms, including dementia, prolonged disease duration, Alzheimer's pattern cognitive impairment, and marked atrophy on imaging.[119] Nevertheless, studies suggest that patients with poor-outcome risk factors can still obtain clinical benefits from shunting and thus should still be offered shunt surgery if otherwise clinically appropriate.[120]

Difficulties in Assessing Clinical Outcomes

There is no established method of quantifying clinical improvement that is standardized, unbiased, and practical.[2] Although clinical outcomes have been reported in the literature using a plethora of scales and variations,[24,28,108] comparisons between these scales can produce markedly different results, even when identical data are used.[2,121] Similarly, outcome studies not only lack randomization but are also generally unblinded, with assessments performed by the treating team, leaving scope for potential bias.

Furthermore, the duration of postoperative follow-up necessary to adequately assess clinical status has not been established.[109] For example, the Dutch NPH study restricted the follow-up period to 1 year,[122] whereas other studies have demonstrated that some INPH patients still continue to improve at 24 months.[9,123] On the other hand, studies that have followed patients for 3 years or more have consistently found declining rates of clinical improvement.[124,125] However, long-term outcomes also undoubtedly are influenced by comorbidities, and vascular factors have been shown to be a main cause of mortality.[126,127] Hence, it is unclear the extent to which this long-term clinical decline is comorbidity-related and not shunt-related.

Methodological Limitations

Unfortunately, these difficulties in INPH research are not just limited to outcome studies. The conclusions and reported predictive values of numerous studies are made unreliable by small sample sizes, retrospective study designs, variable inclusion criteria, and a failure to differentiate INPH from SNPH.[72] Studies are also largely uncontrolled, unblinded, and often lack objective clinical assessments. Furthermore, many studies report positive and negative predictive values that depend on the frequency of disease in the group being studied. Although more difficult to interpret intuitively, sensitivity and specificity are preferable, as they are not influenced by the frequency of disease in the sample. Other useful statistics to estimate effect size, such as Cohen's d, also are rarely reported. Finally, shunt responsiveness does not account for false-positive placebo responders or those who fail to respond due to shunt complications or comorbid diseases.[83] Evidently, there is a need for further research that can address these shortcomings and identify a true gold-standard diagnostic or prognostic measure.

Research into the diagnosis and treatment of INPH has the potential to not only improve clinical outcomes for patients but also to significantly reduce health care expenditure.[128] It has been suggested that the appropriate treatment of hydrocephalus in the elderly may lower 5-year Medicare expenditure by approximately $184.3 million in the United States.[129] It is clear that further translational studies examining the pathophysiology of adult hydrocephalus disorders like INPH are central to improving diagnosis and treatment outcomes. As such, research into these areas has been appropriately identified as a consensus priority for the next 5 years of hydrocephalus research.[63]

Conclusion

After 50 years of research, the diagnosis and treatment of INPH seems to have improved. However, advances continue to be

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hampered by research limitations and shortcomings in our understanding of the pathophysiology underlying INPH. As a result, both the accurate diagnosis of INPH and the appropriate selection of shunt surgery candidates remain controversial issues. Indeed, there is still no universally accepted definition of the syndrome or accepted neuropathological changes. Does this mean we cannot diagnose or treat INPH? We would answer this with a resounding "no." Those familiar with the condition can diagnose it, and most patients so diagnosed obtain meaningful clinical improvement.

Author Roles

1. Research Project: A. Conception, B. Organization, C. Execution; 2. Statistical Analysis: A. Design, B. Execution, C. Review and Critique; 3. Manuscript Preparation: A. Writing the First Draft, B. Review and Critique.

R.S.: 1A, 1B, 1C, 2A, 2B, 2C, 3A, 3B

N.M.: 1A, 1B, 1C, 2A, 2C, 3B

E.J.: 1A, 1B, 1C, 2A, 2C, 3B

B.O.: 1A, 1B, 1C, 2A, 2C, 3B

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