Neurosurgical Review (2020) 43:1451–1464
https://doi.org/10.1007/s10143-019-01201-5

REVIEW

Normal pressure hydrocephalus—an overview of pathophysiological mechanisms and diagnostic procedures

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Received: 18 April 2019 / Revised: 27 September 2019 / Accepted: 25 October 2019 / Published online: 8 November 2019

Abstract

Normal pressure hydrocephalus (NPH) is an important differential diagnosis of neurodegenerative diseases. The prevalence of dementia is increasing in line with the worldwide increase in life expectancy. NPH can be divided into idiopathic (iNPH) and secondary (sNPH) which is important in terms of clinical symptoms, future progress, and the outcome of possible treatment. The full clinical triad is not prevalent in all of the cases and the pathophysiology of iNPH remains unclear. Diagnosis is based on the evaluation of clinical symptoms (Hakim's triad) combined with an MRI assessment, evaluation of CSF dynamic parameters by different methods such as a tap test, lumbar infusion test (LIT), and external lumbar drainage (ELD). Despite the development of diagnostic techniques and strategies in management, NPH remains to be a challenge for the specialists despite more than 50 years of research. However, results of this research have brought new opportunities in the diagnosis, therapy, and quality of life as well as survival time of NPH patients with improved symptoms. The aim of this article is to present the pathophysiological hypotheses of NPH and an overview of the diagnostic techniques used for the evaluation of NPH patients.

Keywords Normal pressure hydrocephalus · NPH pathophysiology · Diagnostic procedures · Idiopathic NPH · Hydrocephalus

Introduction

According to a rise of global life expectancy, especially in the last two decades [87], the prevalence of diseases associated with neurodegenerative processes is increasing. In 2010, the estimated number of people living with dementia worldwide was 35.6 million and this number is expected to rise to 65.7 million by 2030 [92].

Normal pressure hydrocephalus (NPH) plays a role in the differential diagnosis of dementia for more than 50 years as Hakim and Adams described three patients in 1965 who had ventriculomegaly on pneumoencephalography but had no increase in their intracranial pressure (ICP) [38]. They also described a clinical syndrome that consists of a classical triad of symptoms. These are urinary incontinence, dementia, and gait impairment [38]. However, this complete triad is not always seen. In SINPHONI—a Japanese multicenter cohort study looking at the validity of MRI findings in idiopathic NPH (iNPH) [40]—there were only 51% of patients with the complete triad of symptoms. Sexual dysfunction [82], neurological symptoms, psychiatric symptoms, or other infrequently reported signs have circumstantial relation to NPH but may hinder diagnostic processing [99]. Although the prevalence of NPH remains imprecise and is calculated to be 1.30% for those aged ≥ 65 years, a severe problem of underdiagnosis seems to exist [75].

NPH can be divided into primary or idiopathic (iNPH) and secondary (sNPH) [80]. The most commonly used treatment of NPH is implantation of a ventriculoperitoneal (VP) shunt, a system draining CSF from the lateral ventricles to the peritoneal cavity [97]. Shunting leads to a clinical improvement in 70–90% of treated patients in contrast to other, often poorly treatable neurodegenerative disorders [52]. Even though the initial clinical improvement rate is generally high and in some cases may be sustained for up to 5 or even more years [93], the

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long-term outcome studies are limited by a large proportion of patients lost to follow-up which may overestimate the reported rate of clinical improvement (average of 65% of cases in at least 3 years after surgery in a systematic review by Toma et al. (2013)) [114] [10]. It is difficult to determine the reasons of lost of follow-up and almost impossible in retrospective studies. The evaluation of iNPH is not an easy task. Some of the patients may die or fail to recognize the returning symptoms or to seek attention for them, fail to return because symptoms remain under control, feel that the follow-up is unnecessary [93], or even might be mistakenly diagnosed with iNPH and instead of it suffer from a developed neurodegenerative disease. [26]

In a recent meta-analysis of 33 studies, complication rate of VP shunting ranged 13–38%, 26–38% of cases shunted with a fixed-pressure valve and 9–16% of cases shunted with an adjustable valve required a revision surgery as the only significant difference between both groups [34].

The lack of sustained follow-up, risks of shunt malfunction, and the rate of shunt complications and revisions remain to be drawbacks of the outcome of shunting in NPH. However, it has been reported in a Swedish cost-utility analysis on 30 patients diagnosed with iNPH based on clinical and radiological criteria only that an average patient gains 1.7 quality-adjusted life-years (QALY) after shunting which is significantly higher than that in Alzheimer's disease (AD) patients treated with donepezil (0.11 QALY) or patients suffering from acute stroke treated with endovascular thrombectomy (0.99 QALY) [116].

Diagnosis is based on clinical symptoms combined with diagnostic procedures. In a recent survey [22] of up to 30% of patients who fill the MRI criterion of hydrocephalus, Hakim's triad was not fully expressed while the tap test was negative and CSF outflow resistance was low. This makes NPH diagnosis a difficult task with a possible lack of reliability while there is a speculative subsequent prediction of shunt response in accordance with a poor knowledge of iNPH pathogenesis. Up to 80% of NPH patients remain unrecognized [52] and thus, their medical treatment is inappropriate.

Methods

We searched the MEDLINE, EMBASE, and Cochrane library (Cochrane reviews, Cochrane central register of controlled trials) databases for the literature. We also reviewed the reference lists of the included articles. The last search was run on 2 February 2019. We used the following keywords to search the databases: "normal pressure hydrocephalus," "idiopathic normal pressure hydrocephalus," "hydrocephalus," "cerebrospinal fluid drainage," "CSF," "tap test," "nph diagnosis," "nph pathophysiology," "lumbar infusion test," "external lumbar drainage." We reviewed the titles and abstracts and those related to normal pressure hydrocephalus were included. Irrelevant studies not pertaining to this query, grey literature publications, Commentaries, Letters, and Editorials were excluded (Fig. 1).

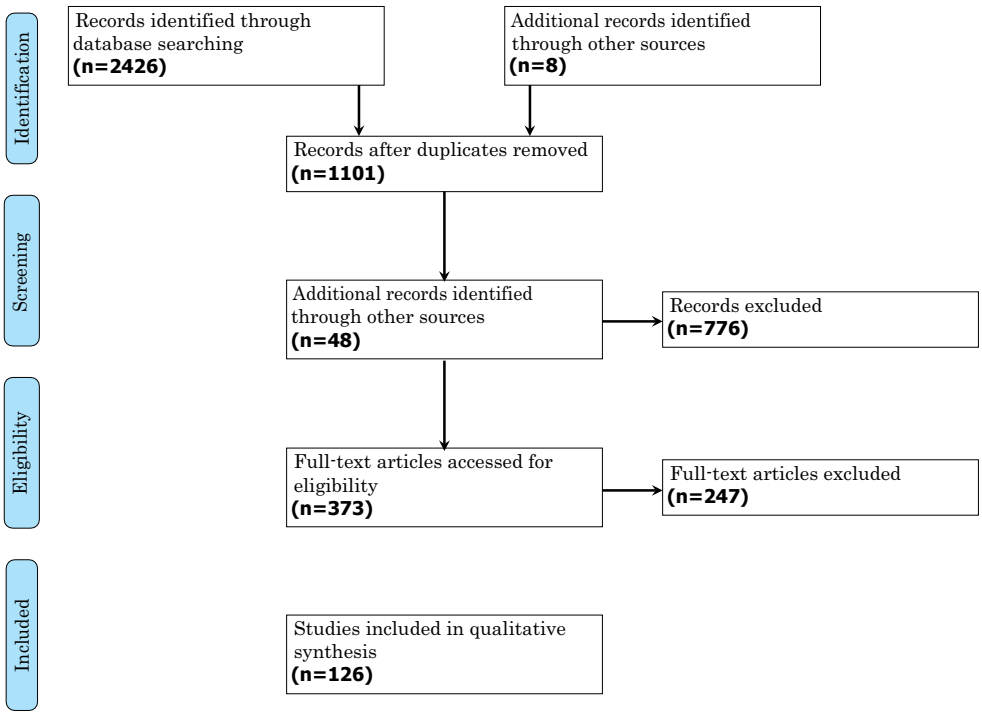


Fig. 1 The flow diagram describing literature search process.

Pathophysiology of NPH

Normal pressure hydrocephalus can be divided into two different entities—idiopathic (iNPH), where the underlying cause is not previously known, and secondary (sNPH), which can be a result of various pathologies such as subarachnoid hemorrhage, trauma, meningitis, malignancy, stroke, and intracerebral hemorrhage [25]. Marmarou et al. (2005) [74] reported that the combination of cases of iNPH and sNPH may lead to considerable controversy in the diagnosis and therapy of such cases.

In the case of sNPH, fibrosis and adhesions in the subarachnoid space and arachnoid granulations can lead to NPH [25]. Products and cellular components of intracranial tumors [89] or proteins and cells from subarachnoid hemorrhage or meningitis may lead to an increase of CSF viscosity and impairment in CSF reabsorption. Both mechanisms lead to an initial increase in the CSF pressure resulting in ventricular enlargement. A new balance between CSF pressure and volume occurs in the CSF space [25]. SNPH may affect every age following the initial incident while iNPH occurs most commonly in the elderly population [25]. The preclinical stage of sNPH is typically much shorter, over weeks or months [72], than the preclinical development of iNPH, which is gradual over years.

In sNPH, the neurological deficits caused by the primary diseases may mask the typical NPH symptoms [18]. However, it was reported that the outcome of shunt surgery was significantly better for sNPH than for iNPH patients while the disease duration of less than 1 year was an important factor [111]. Valve adjustments were found to be more frequent in iNPH than in sNPH cases (49% vs. 32% reported by Zemack and Romner, 2002) [126].

Pathophysiology of iNPH

The first theory defining the pathophysiology of iNPH was published over five decades ago [38]. Over the years, alternative hypotheses to clarify the pathophysiological mechanisms behind this disease have been published (Table 1). Yet, none of them has found a unifying concept to explain these and fundamental questions have still not been answered. INPH may not even be an entity by itself and symptoms and pathogenetic mechanisms resulting from different geneses might be included under the term iNPH [16]. Also, there may be a role of an impairment of the recently discovered glymphatic pathway but further investigations clarifying its function in humans [95] and its implication to neurodegenerative processes are needed [6]. Altered aquaporin 4 expression in astrocytic perivascular endfeet is evident in brain tissue of AD and NPH patients and MRI scans of NPH patients show reduced CSF tracer entry and clearance [28, 39]. On the basis of MRI imaging with intrathecal administration of gadobutrol in 15 iNPH patients and 8 controls, Ringstad et al. [101] hypothesized that the restricted arterial pulsations reduce glymphatic flow leading to the reduction of transport of solutes and CSF through the glymphatic pathway and further reduce intracranial compliance and the obstruction between the paravascular and interstitial spaces may be responsible for retrograde transventricular route of CSF flow. According to the overnight peak of parenchymal gadobutrol enhancement [101] and their reported frequent association of obstructive sleep apnea (OSA) and iNPH (90.3% of iNPH patients had an associated OSA), Román et al. [103] discussed a potential role of sleep-disordered breathing in the iNPH pathophysiology.

Table 1 List of different iNPH theories (based on Ammar et al. (2017) [5] and Krishnamurthy and Li (2014) [60])

1. Hakim-Adams theory (Hakim and Adams 1965) [38]
2. Transcerebral mantle pressure gradient (Hoff and Barber 1974) [44]
3. Restricted arterial pulsation hydrocephalus (Greitz 1993) [37]
4. Bulk flow theory (Rekate 1988) [98]
5. Unifying theory for definition and classification of hydrocephalus (Raimondi 1994) [94]
6. Hemodynamic theory of venous congestion (Bateman 2004) [7]
7. Evolution theory in cerebrospinal fluid dynamics and minor pathway hydrocephalus (Oi and Di Rocco 2006) [86]
8. Importance of cortical subarachnoid space in understanding hydrocephalus (Rekate 2008) [98]
9. Pulsatile vector theory (Preuss et al. 2013) [91]
10. Reassessing CSF hydrodynamics and novel hypothesis (Chikly B. and Quaghebeur J. 2013) [19]
11. Osmotic gradient theory (Krishnamurthy and Li 2014) [60]
12. Intimate exchange between cerebrospinal fluid and interstitial fluid. (Matsumae et al. 2016) [77]
13. The Comprehensive Idiopathic Normal-Pressure Hydrocephalus Theory (CiNPHT) (Ammar et al. 2017) [5]

Before the advances in the research of glymphatic system, Ammar et al. (2017) [5] reviewed existing theories and created a new concept which summarizes the previously discovered findings into a complex system which connects different pathophysiological mechanisms. This system works as a vicious cycle, where one mechanism determines the other. The goal of current therapeutic options is to disrupt this vicious cycle which, despite all efforts, can only slow down.

Ventricular enlargement is accompanied with a slow CSF flow to subarachnoid space and its impaired absorption which is exceeded by the production. The dilatation increases mechanical stress on the periventricular white matter, causing ischemia and hypoxia in the white matter axons [2]. Chronic healing attempts can lead to decreased brain compliance around the ventricle, which results in "stiff ventricles" [5]. The ependymal layer progressively loses plasticity while pulsatility is concurrently

significantly reduced [37]. This further leads to an impairment of bulk flow through the outlets of the CSF compartments [98]. The expansion of the ventricles will cause pressure on a larger surface area and if the pressure exceeds the elastic tension of the surrounding brain tissue, the ventricles enlarge again and the pressure falls to normal values [38]. Despite the normal pressure in the ventricles, the force on ventricular wall is greater and proportional to the increased surface area [51]. Concurrently impaired blood flow, hypoxia, and ischemia lead to metabolic and biochemical disruptions [59]. Subsequently, demyelination and neural apoptosis occur as a final result. Interstitial fluid accumulates and the transmantle pressure is increased [44] possibly leading to venous congestion, hindrance of intraparenchymal CSF pathways and worsening of transependymal transudation. The increased interstitial fluids and pressure cause damage to the neural and glial cells, alteration of biochemical processes, increased oxidative stress, blockage of oligodendrocyte differentiation, and glial scars [76]. Congested veins lead to a decreased drainage of the brain leading to increased accumulation of the toxic elements [7]. Compression or occlusion of small blood cells causes ischemia, the tissue loses integrity and became stiff, compliance is reduced, and transmission of pulsatile waves is decreased [91]. The CSF is produced at the same rate but the flow through is delayed; the ventricles dilate more which worsens the lesions in surrounding brain tissue which further slows down the flow [5].

In context of the studies clarifying cellular and molecular abnormalities leading to ciliary dysfunction of ependymal cells in congenital hydrocephalus associated with primary ciliary dyskinesia [63], a recent discovery has been made in a Japanese family with multiple individuals with NPH. A loss of product of CFAP43 gene is suggested to be related to morphologic or movement abnormalities of cilia in the ependymal or choroidal cells and is associated with the NPH in these individuals in a heterozygous state. This could be helpful in the elucidation of the pathogenesis of iNPH but more research on cellular dysfunction has to be done [84].

Despite all the currently known characteristics of CSF flow, cerebrovascular system, and brain environment, there is still a lot to be clarified in the pathophysiology of iNPH in correlation with autopsy findings, diagnostic methods, clinical examination, and treatment options to offer an optimal therapy and management of iNPH patients [60, 65].

Natural history of iNPH

The main symptoms of Hakim's triad do not have to be present together and their onset, severity, and progression are variable [99]. The progression can vary but most of the reported cases of iNPH patients without or postponed shunt surgery had deteriorated during the first few months after initial assessment [113]. INPH is a lifelong disease. Shunt insertion may permanently relieve symptoms but cannot eliminate the chain of the currently poorly known causes of the disease [67]. A systematic review of 30 studies of ventriculoperitoneal shunting showed similar rates of symptomatic improvement after 3 months and 1 year [114] but after the initial improvement, the symptoms relapse despite evidence of a functioning shunt. This is increased in older patients and over the time, the symptoms progress due to the underlying neurodegenerative process [10]. Mirzayan (2010) [81] found no statistically significant difference between outcomes at 18 and 81 months, but many patients were lost to follow-up or died.

Differential diagnosis of NPH

The differential diagnosis (Table 2) includes a high number of diseases that are more or less common in elderly patients. The clinical symptoms of NPH may be subtle and may resemble other neurodegenerative disorders [33], primary urological disorders, vascular dementias, other hydrocephalus conditions, infectious diseases, result of traumatic insult, brain or spinal tumors, metabolic conditions, and organ failures such as dialysis dementia, Wilson's disease, hepatocerebral degeneration and many other diseases [99, 100].

A different condition may be concurrent with NPH—most commonly AD or vascular dementia [9]—and the presence of comorbidity is a statistically significant predictor of shunt therapy outcome in iNPH. This may be evaluated using various tools such as the comorbidity index (CMI) [79]. Characterization of the diseases or wider comparison with clinical symptoms of NPH and its possible diagnostic procedures used to evaluate these diseases (Table 2) is beyond this article. However, a sound knowledge of the etiologies, diagnostic procedures, and possible treatment is needed for an appropriate clinical approach to these disorders. It is important to identify the signs of possible NPH in the evaluation of these diseases and, with further testing, choose the patients who would benefit from shunting. Because the elderly population of NPH patients is prone to the comorbidities mentioned in this article, it is almost impossible to see "pure" NPH [123]. The influence of these diseases on the outcome of shunting could be very large, so a complex testing battery is needed to identify the signs of other disorders and treat the treatable ones—for example resting tremor during clinical exam, hesitance during gait assessment (Parkinson's disease or Lewy body dementia), rapid forgetting of newly acquired information during neuropsychology assessment (Alzheimer's disease), joint pain during gait assessment (arthrosis), and dysuria in the urinary symptoms assessment (urinary tract infection, bladder cancer) [71]. Only with such approach can benefit to these patients be achieved.

Table 2 Differential diagnosis of Normal pressure hydrocephalus including comorbidities and potential causes of sNPH (based on Relkin et al. (2005) [99] and Rigamonti et al. (2014) [100])

Vascular dementias	*Other hydrocephalus conditions*
Cerebrovascular disease	Obstructive hydrocephalus*
Stroke	LOVA
Binswanger's disease	Arrested hydrocephalus
Multi-infarct dementia	Aqueductal stenosis*
Subcortical infarcts	
Leukoencephalopathy	
Cerebral autosomal dominant arteriopathy	
Vertebrobasilar insufficiency	
Infectious diseases	*Urological diseases*
Lyme borreliosis	Bladder or prostate cancer
Human immunodeficiency virus	Benign prostatic hyperplasia
Progressive multifocal leukoencephalopathy (PML)	Stress incontinence or pelvic
Floor laxity syphilis	Urinary tract infection
Neurodegenerative diseases	*Miscellaneous*
Alzheimer's disease	Epilepsy
Parkinson's disease	Depression
Lewy body disease	B_{12} deficiency
Frontotemporal dementia	Collagen vascular disorders
Corticobasal degeneration	Spinal stenosis
Progressive supranuclear palsy	Chronic traumatic brain injury
Amyotrophic lateral sclerosis	Chiari malformation
Huntington's disease	Wernicke's encephalopathy
Spongiform encephalopathy	Carcinomatous meningitis
Multisystem atrophy	Spinal cord tumor
	Brain tumor
	Hypothyroidism
	Organ failures
	Peripheral neuropathy
	Chronic subdural hematoma

LOVA, long-standing overt ventriculomegaly syndrome

*Obstructive hydrocephalus may be due to the obstruction in different parts of the CSF pathway not only in the aqueduct. To point out the differences between these entities, many clinicians use aqueduct stenosis as a separate disease with respect to the pathogenesis; hydraulic mechanisms of compensated states, chronic, subacute, or acute courses; and the degree of the stenosis which in a specific state can be responsible for NPH clinical symptoms [102]

Diagnostic techniques and procedures

Gait assessment

Gait disturbance is typically the first clinical manifestation of NPH and also the most responsive feature to shunting [93]. The NPH gait is characterized by reduced speed, short steps, reduced step height, and impaired dynamic equilibrium with accented expression during turning [74] and is often described as "magnetic" or "glued to the floor" [33]. Enlarged step width, larger foot angles, and no improvement of walking with visual and/or acoustic cues were also described [109]. Patients may also experience difficulty in rising from a chair or walking on stairs [99]. Postural dysfunction is another prevalent finding, which results in a forward leaning posture with provoked or spontaneous backward falling [115]. Blomsterwall et al. (2000) [11] were interested in the correlation between both gait and balance impairment before and after shunt surgery. They found that improvement in balance may partly be responsible for the improved gait (75% of patients improved walking speed and 69% balance).

Gait evaluation often consists of both subjective and objective measurements. The subjective rating scales may include categorical (e.g., bedridden, walk but unstable) [90] or specific ratings (e.g., tandem walking disturbed) [96]. Objective measurements may provide more reproducible and rigorous assessments. Clinicians may observe cadence, step height, step width, stride length, tandem gait, shoulder-hip counter-

rotation, turning, resting sway, posture, start hesitation, and retropulsion in a specific defined manner [115]. The use of a Timed Up and Go test in gait evaluation of NPH patients showed high sensitivity and specificity for the prediction of functional improvement at 1 year after VP shunt surgery and lumboperitoneal (LP) shunt surgery, where VP shunt conveyed better improvements in this gait evaluation method [125]. Other methods include observation and descriptive assessment of gait using videotapes [74] or tests such as 10-m walk test, Berg balance scale, Tinetti scale [31], or GAITRite system [124].

Neuropsychology

The cognitive profile of NPH is comprise of an alteration in working memory, learning, attention, processing speed, psychomotor speed, executive, visuospatial, and visuoconstructional functions [45]. In comparison with AD which is a "cortical dementia," NPH is a "subcortical dementia" [117]. This term refers to a mental decline arising from the impairment of subcortical structures resulting in slowed processing speed and apathy [55]. Frontal functions (such as executive functions) are also disrupted due to damage of fronto-subcortical projections or subcortical structures and are more severely impaired in comparison with AD while memory is presented by delayed recall and delayed recognition [120] and is less affected compared with AD [85]. Iddon et al. (1999) [45] examined a group of NPH patients (MMSE ≥ 24, $n = 6$) using CANTAB (Cambridge neuropsychological test automated battery). These patients were impaired in spatial recognition but unimpaired in pattern recognition compared with healthy controls. This supports the relation of fronto-subcortical changes to the cognitive profile shown in NPH patients [27, 45]. However, as mentioned above, the prevalence of comorbidities is very high. We assume that the "true" cognitive profile of iNPH can only come from prospective studies with autopsy-proven NPH in the absence of other well-developed neurodegenerative diseases.

Neuropsychology assessment is a non-invasive and inexpensive tool for objective measurement of cognitive and behavioral symptoms of NPH [27] and may also be used to predict shunt response if it follows specific patterns [110]. Various neuropsychological batteries for cognitive, behavioral, and emotional evaluation of NPH patients have been developed [43] even combined with gait, balance, and incontinence assessment in iNPH scale [43]. These batteries often consist of well-validated neuropsychological procedures such as Mini Mental State Exam (MMSE), Rey's Auditory Verbal Learning Test (RAVLT), Rey-Osterrieth Complex Figure Test (ROCFT), Controlled Oral Word Association Test (COWAT), Block Design Test (BDT), and Geriatric Depression Scale (GDS), Trail Making Test (TMT; trail A and trail B). Each of these tests targets different aspects of NPH cognitive and behavioral profile.

Assessment of urinary symptoms

The lower urinary tract symptoms (LUTS) are prevalent in a population older than 60 years. The epidemiologic EPIC study [58] reported prevalence of any LUTS in 94% of men and 89% of women and prevalence of overactive bladder (OAB) in 28% of men and 34% of women in population aged ≥ 60 years in the Czech Republic.

According to the International Continence Society, a standardized terminology for urinary symptoms is recommended. Overactive bladder is defined as a urinary urgency with or without urge incontinence and is usually associated with frequency and nocturia [56]. The constellation of all these symptoms is called "storage" or "irritative" symptoms. The constellation of straining, intermittent stream, slowed stream, post-void dribbling, and hesitancy is often termed "voiding" or "obstructive" symptoms [100]. Lesions above the pontine micturition center cause a lack of inhibitory control of the bladder and result in detrusor overactivity with or without incontinence which was described in NPH patients [104]. The proximity of some of the centers that control micturition or their connecting pathways to the ventricular system may result in the urinary symptoms in NPH [115].

Subjective information provided through validated questionnaires developed by the International Consultation on Incontinence Modular Questionnaires (ICIq) has become an accepted mean to standardize the assessment of urinary symptoms and outcome measurement [62]. However, urodynamic testing may be the most important investigative procedure. In this study, the patient is placed on a specialized chair with an infusion of saline through a urinary catheter. An additional catheter is placed in the rectum or the vagina for the simultaneous measurement of intravesical and intraabdominal pressure [100], maximum flow rate, post-void residual, bladder capacity, first sensation, and detrusor activity [61]. The function of the urethral sphincter is measured with an electromyography [56]. The common finding in NPH patients is typically detrusor overactivity, possibly responsible for urinary urgency which is thought to precede urge incontinence in the progression of iNPH [104].

Lumbar infusion test

The consensus of experts combined limited published works to establish the expected range of iNPH opening pressure between 4.4 and 17.6 mmHg [73]. A single measurement of ICP is limited for the diagnosis and outcome; therefore, it is preferable to use CSF dynamic studies to evaluate NPH [73]. One of them is the Lumbar Infusion Test (LIT) with a modification of the technique originally described by Katzman and

Hussey in 1970 [15]. In the LIT, ICP is continuously measured during a constant infusion of artificial CSF or saline into the lumbar subarachnoid space via a lumbar needle (Fig. 2). The flow is applied against the ICP. This flow may determine parameters of CSF dynamics such as the conductance or reciprocal outflow resistance (R_{out}) which is the most important one in most of the LIT protocols [78]. There is a nonlinear correlation between the increase of ICP with increasing R_{out} which is defined as the difference in the final steady-state pressure and the initial pressure divided by the flow rate of infusion [12]. A widely accepted threshold of R_{out} is not established but the value of 12 mmHg/ml/min seems to be the most suitable threshold [54]. Also, research on healthy volunteers has shown that R_{out} does not normally exceed 10 mmHg/ml/min [3].

The sensitivity of LIT between 56 and 100% and specificity between 50 and 90% have been reported in various publications [42]. The positive predictive value of LIT is 80% and the occurrence of false-negatives is up to 16% [50].

Tap test

In the description of NPH by Hakim and Adams in 1965 [38], three patients had 15 ml of CSF removed via a spinal tap with improvement of symptoms in all these patients. Since this reference, many clinicians have used lumbar punctures with the removal of CSF to identify potential shunt responders. However, the borderline of significant improvement has not been formalized [73]. Removing CSF from the subarachnoid space lowers the ICP and CSF resorption for several hours with a possible partial normalization of CSF hydrodynamics [121]. Currently, in a tap test (TT), 30–50 ml of CSF is drained from the patients with a following assessment of symptom improvement [32]. Recent research is focused on clinically used gait, balance, and cognition evaluation methods that can identify improvement from a TT [32].

The positive predictive value of TT between 73 and 100%, sensitivity between 26 and 62%, and specificity between 33 and 100% have been reported in various studies [73]. Therefore, negative results of TT cannot be used to exclude patients from treatment [122].

External lumbar drainage

External lumbar drainage (ELD) is recommended for the evaluation of NPH [120]. The effusion rate varies between 5 and 10 ml/h while the patient is in a horizontal position and the drainage is closed before the patient gets up. The drainage is maintained for 3 to 5 days [73]. The positive effect of ELD can be demonstrated with phase-contrast MRI with CSF flow change in the cerebral aqueduct [107]. The rate of significant complications was reported to be 3% [35].

The positive predictive value of ELD between 80 and 100%, sensitivity between 50 and 100%, and specificity between 60 and 100% have been reported in various studies (Table 3) [73].

In accordance with the statistical values (Table 3), a single predictive for shunting cannot be derived from the invasive procedures to the individual patient. This may be due to the complex pathogenesis of iNPH [70] together with the complexity of intracranial pressure and CSF hydrodynamics [23]. However, ELD seems to have the best and most reasonable prognostic accuracy for the prediction of shunt responsiveness in iNPH patients [20]. According to the reported statistical values (Table 3), we suggest to perform LIT with a subsequent ELD in the evaluation process.

Imaging modalities

Imaging techniques are used in the management of iNPH including CT and MRI for visualization of ventricle expansion and conventional X-rays or radionuclide shunt patency studies

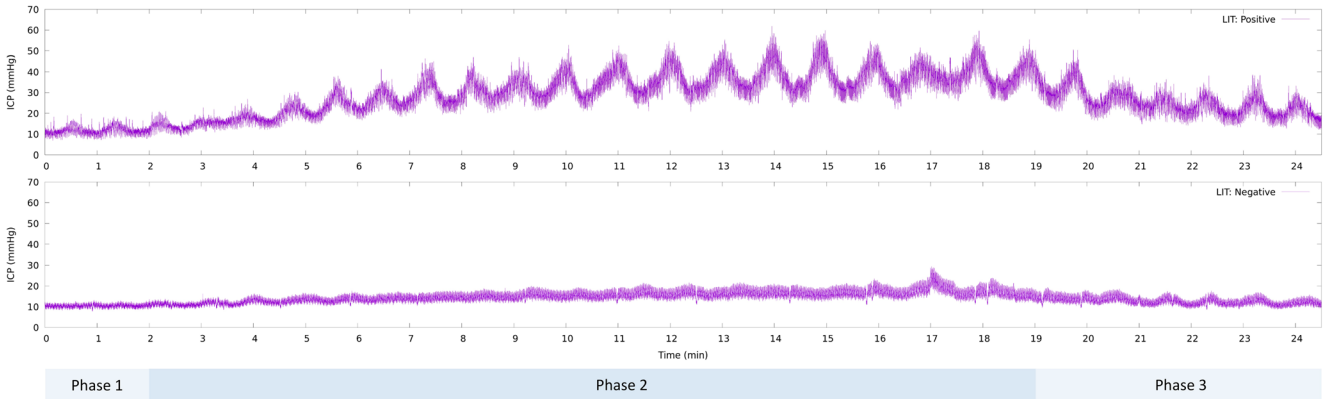


Fig. 2 Comparison of the positive (top) and negative (bottom) lumbar infusion test. The ICP (mmHg) is recorded throughout three subsequent phases. Phase 1: equilibration of the CSF pressure, infusion pump is off (first 2 min); phase 2: infusion of Ringer's solution until a stationary state, ICP plateau is reached, infusion pump is on (approx. 13–20 min); phase 3: recovery of the initial ICP state, infusion pump is off (approx. 4–6 min). Of note are the low-frequency oscillations of the elevated ICP expressed especially in the LIT-positive patient

Table 3 Summary of reported statistic values for LIT, TT, and ELD [42, 50, 73]

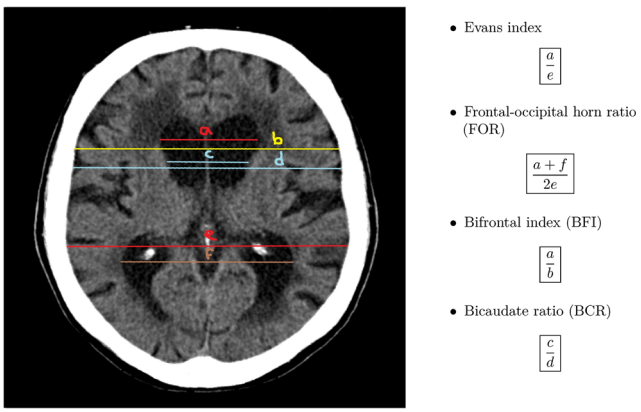
	Sensitivity (%)	Specificity (%)	Positive predictive value (%)
Lumbar infusion test	56–100	50–90	80
Tap test	26–62	33–100	73–100
External ventricular drainage	50–100	60–100	80–100

for the evaluation of shunt malfunction [64]. However, it is not possible to diagnose NPH using MRI or CT only. The size of the ventricles does not correlate with flow resistance, resting pressure and pressure-volume index [13].

Various indices (Fig. 3) are used in clinical practice to evaluate ventriculomegaly in NPH patients. Evans index, which was introduced by William A. Evans in 1942 [29], is a standard. It describes the widest distance in the frontal horns divided by the widest transverse distance between the tabulae internae. However, values of the Evans index can significantly vary depending on the level of the brain CT scan image [112] and the volumetric analysis could be more accurate [112]. Other indices such as frontal-occipital horn ratio (FOR), bicaudate ratio (BCR), or bifrontal index (BFI) [8] were introduced, but their use is uncommon. Specific method using CT – CT cisternography is obsolete due to its invasiveness and false-positive results in more than 60% of cases [14].

Postoperative CT scan is important for the description of results and potential complications of shunt surgery. Routine follow-up is often 3, 6, and 12 months and then annually after shunt implantation [66]. However, many authors state that CT scans are not required after 1 year of follow-up period as long as the clinical symptoms are not severely changed [57] as the change in ventricular size does not correlate with the clinical outcome of therapy [80].

However, the images of MRI are more detailed. MRI provides an easier detection of special conditions (aqueduct stenosis), better description accuracy of radiological signs of NPH (Fig. 4). One of these is the presence of "disproportionately enlarged subarachnoid space hydrocephalus" (DESH),



- Evans index $\frac{a}{e}$
- Frontal-occipital horn ratio (FOR) $\frac{a+f}{2e}$
- Bifrontal index (BFI) $\frac{a}{b}$
- Bicaudate ratio (BCR) $\frac{c}{d}$

Fig. 3 CT scan of a suspected iNPH patient with equations for calculating various indices

which was proposed to be a pathognomonic feature of iNPH by the Japanese Guidelines [83]. DESH is composed of three components: ventriculomegaly, high convexity tightness, and enlarged Sylvian fissure [48]. The role of DESH in the identification of shunt responders remains controversial [21, 119] although multiple studies presented results that could indicate this fact [40, 119]. The presence of DESH without clinical symptoms has been termed asymptomatic ventriculomegaly with features of idiopathic normal pressure hydrocephalus on MRI (AVIM) and some authors describe it to actually be a preclinical state of iNPH [46]. Another diagnostic feature which could be described on MRI image is a callosal angle (CA). Value of the CA was found to be significantly lower in iNPH patients than that of AD and control groups [47]. The measurement of the CA should be done on a coronal image perpendicular to the AC-PC plane at the level of posterior commissure [118] as well as the description of DESH [83]. The CA may be another non-invasive tool to help predict shunt responsiveness [36, 118]. A cingulate sulcus sign has also been proposed to be a feature of iNPH. It denotes posterior part of cingulate sulcus being narrower than the anterior part with a divider between both parts being a line parallel to the floor of the 4th ventricle [1].

MRI may also provide potential specific protocols such as phase-contrast MRI with the measurement of CSF flow rate in the cerebral aqueduct [76]. CSF flow rate in the cerebral aqueduct has been clinically evaluated by fMRI using the 2D phase-contrast technique with a CSF flow rate of more than 24.5 ml/min with high specificity for NPH (95%) but low sensitivity (46%) and currently is not reliable for prediction of shunt surgery outcome [4]. Aqueductal flow void which is a decrease of signal seen within the aqueduct on T2-weighted images resulting from greater outflow of CSF was found to be correlated with shunt results in the first studies but later studies found that single PC-MRI measurement or CSF flow void alone cannot safely support NPH diagnosis or shunt responsiveness because it has been observed even in healthy individuals [24].

Another interesting area of MRI is diffusion tensor imaging (DTI) with potential future value. Using DTI, specific microstructural changes in periventricular white matter have been reported [41], changes in the frontal white matter could impair signaling between the frontal cortex and basal ganglia [68], and higher fractional anisotropy in the posterior limb of the internal capsule could possibly explain gait symptoms of iNPH [53]. Magnetic resonance elastography which visualizes

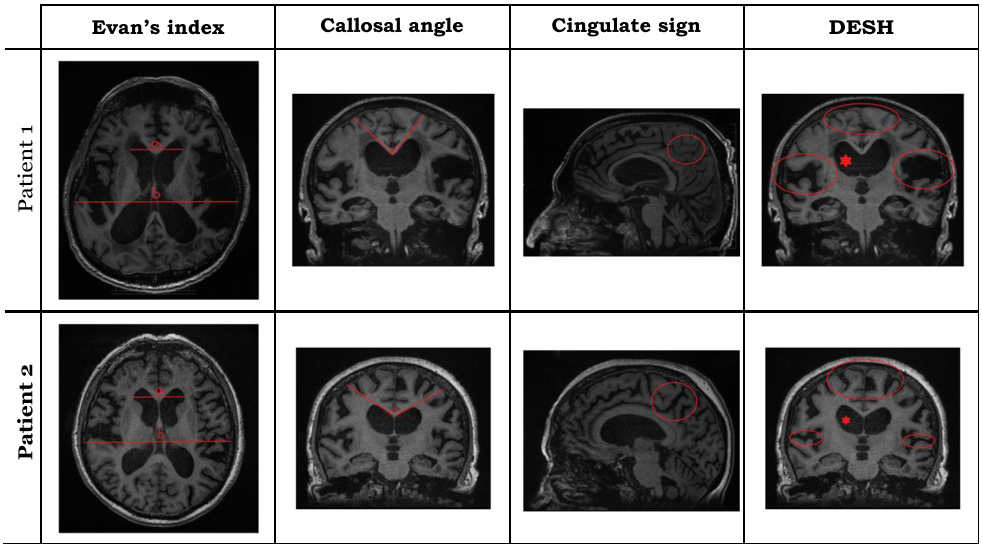


Fig. 4 MRI findings (T1WI) in two patients positive for Hakim's triad. Both patients had ventriculomegaly (Evan's index = 0.35). Patient 1 (male, 75 years) had an acute callosal angle (= 85°), positive cingulate sign, and disproportionately enlarged subarachnoid space hydrocephalus (DESH). All of these were suggestive of iNPH. Patient 2 (female, 77 years) had an obtuse callosal angle (= 115°), negative cingulate sign, and an absence of DESH. Patient 1 was positive in both LIT and ELD and he was offered implantation of a VP shunt. Patient 2 was negative in both functional tests and VP shunting was not indicated

elasticity of the brain has also a possible future benefit in iNPH evaluation; e.g., significant decrease of viscoelastic properties near the ventricles has been reported [30].

Laboratory findings

Nowadays, there are no disease-specific biomarkers used in clinical practice for evaluation of iNPH. However, recent publications defined potential candidates [49, 69, 105, 106] as well as theories explaining such findings [49]. Li et al. (2006) [69] consider the leucine-rich α-2-glycoprotein (LRG) to be specific for iNPH. Also, other biomarkers of subcortical damage, namely neurofilament light chains (NFL) and myelin basic protein (MPB), are increased in the CSF of iNPH patients but the specificity of all of these three markers was found to be limited [106]. Reduction of amyloid-β-related proteins is associated with reduced or normal p-tau and t-tau in iNPH, while in AD, a reduction of amyloid-β-related proteins is coupled with an increase of p-tau and t-tau [105]. However, interpretation is difficult because of the high concurrence of both diseases [17]. Inflammatory biomarkers (TGF-β1, IL-1β, IL-6, IL-10) are potentially increased, but there is currently no evidence for their validity in evaluation of iNPH [106]. Neurosteroids (pregnenolone, PREG; dehydroepiandrosterone, DHEA; their sulfates and metabolites) appear to be promising analytes in the search for a signature NPH biomarker. In a study by Sosvorova et al. (2015), the proposed OPLS model absolutely discriminates NPH based on CSF steroids and neurosteroids [108]. However, none of the known biomarkers is currently clinically used for predicting shunt responsiveness [88] and further investigations are needed [106].

Conclusion

NPH is an important differential diagnosis of neurodegenerative disorders. It can be divided into iNPH and sNPH. More than 50 years of research did not completely clarify the pathophysiology of iNPH; however, it seems that iNPH is a vicious cycle of different underlying pathophysiological mechanisms. iNPH affects the elderly and many of them have other comorbidities. If these are not sufficient to explain the patients symptoms, iNPH should be considered. The presence of comorbidities does not exclude the iNPH patients from shunting; however, the outcome of shunt surgery is strongly influenced by these disorders; thus, the important part of the iNPH management is to identify any of the treatable conditions.

The diagnostic procedures used in NPH evaluation process include gait, urinary, and neuropsychological assessment which are used to identify characteristic clinical features of the disease. Lumbar infusion test, spinal tap test, and external lumbar drainage explore the CSF hydrodynamics and specific radiological signs are identified during imaging procedures. The laboratory findings are not used in clinical practice and their validity needs to be confirmed by future studies. However, potential candidates such as neurosteroids or identification of different biomarkers in a complex laboratory protocol may possibly provide a valid diagnosis of NPH. Recent research is focused on identification of shunt responders. Callosal angle, DESH, cingulate sulcus sign on the T1W1 of

MRI images, or positive external lumbar drainage seems to be most promising in the evaluation of outcome after shunt implantation. However, the disease itself is a complex entity and it turns out that the successful therapy of NPH requires thorough consideration of the results of different diagnostic procedures to achieve an improvement of survival and quality of life of NPH patients. In spite of putative and supposed pathogenesis of the iNPH that is hindering the care of the patients, its current treatment is more successful than the treatment of other neurodegenerative diseases despite the potential risks of complications, shunt failure rates, or needs for surgical revisions that may reduce its socio-economic benefits.

Funding information This study is supported by an institutional grant from the Czech Ministry of Defence MO1012.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval For this type of study formal consent is not required.

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