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Chapter

Normal Pressure Hydrocephalus: Revisiting the Hydrodynamics of the Brain

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Abstract

Normal pressure hydrocephalus syndrome is the most common form of hydrocephalus in the elderly and produces a dementia which can be reversible surgically. It is characterized by ventriculomegaly and the classic triad of symmetric gait disturbance, cognitive decline and urinary incontinence, also known as Hakim's triad. To date, the exact etiology of the disease has not been elucidated and the only effective treatment is a cerebrospinal fluid shunting procedure which can be a ventriculoatrial, ventriculoperitoneal or lumboperitoneal shunt. The most important problem is the high rate of underdiagnosis or misdiagnosis due to similarities in symptoms with other neurodegenerative disorders, and in some cases, coexistence. Hence, increasing awareness amongst the community and medical professionals in order to increase clinical suspicion, timely diagnosis and treatment are paramount. The best way to achieve this is by having a structured protocol with patient-centered tests that evaluates the entire myriad of alterations a clinician might encounter whenever treating patients with this disorder. Recent advances in imaging technology as well as cerebrospinal fluid biomarkers have given interesting insight into the pathophysiology of the disease and will certainly contribute greatly in diagnostic advancements. We finally present an institutional protocol which has been accredited by international peers with promising results in diagnostic and outcome rates.

Keywords: Normal pressure hydrocephalus syndrome (NPH), cerebrospinal fluid (CSF), ventriculoatrial shunt (VAS), ventriculoperitoneal shunt (VPS), lumboperitoneal shunt, intracranial pressure (ICP), lumbar puncture (LP), center of excellence (COE)

1. Introduction

Normal Pressure Hydrocephalus (NPH) is a type of chronic communicating hydrocephalus recognized as the most common form of hydrocephalus in the elderly with an estimated prevalence of 5.9% in those aged over 80 years [1]. NPH was first described by Hakim in 1965, hence, it is sometimes found as Hakim's syndrome. NPH is characterized by enlarged brain lateral ventricles

(ventriculomegaly) with normal cerebrospinal fluid (CSF) pressure and the classic clinical triad of symmetric gait disturbance, gradually progressive cognitive decline, and urinary incontinence, also known as Hakim's triad [2].

In this chapter, we present a concise review of all available evidence regarding epidemiology, pathophysiology, diagnostic and treatment methods including some diagnostic novelties that could be determinant sometime in the near future.

2. Epidemiology

NPH is the main cause of surgically reversible dementia in the population aged 50–80 years with a global estimated prevalence of 0.2% in the group aged 70–79 years and 5.9% in those over 80 according to epidemiologic studies in Sweden [1]. However, the estimated prevalence reported by populated-based studies in Japan is 1.6% [3–6]. If surveys in Sweden had used diagnostic criteria in Japanese guidelines, their weighted average would have been 1.5% [7]. These data may underestimate the actual prevalence and incidence because some studies have flawed methodology and use different criteria. The prevalence and incidence of any hydrocephalus, especially NPH, will increase as mean life expectancy increases. Mortality associated with untreated hydrocephalus ranges from 20 to 87% depending on the etiology [8]. Therefore, diagnosing and treating chronic hydrocephalus is a public health problem that requires attention and active participation of the entire scientific community and health personnel.

NPH is a condition with a high rate of underdiagnosis because it can be confused with other types of dementia, especially Alzheimer's dementia (AD) and Parkinson's disease, and because in many cases there is simply no clinical suspicion by medical staff. Approximately 5–10% of patients with some type of dementia may suffer from chronic hydrocephalus and another concomitant disorder such as AD, frontotemporal dementia (FTD), subcortical arteriosclerotic dementia (SAD) also known as Binswanger's disease, Lewy bodies dementia, amongst others. In fact in epidemiologic studies, 24% of patients with clinical suspicion of NPH had typical histopathologic findings of AD in brain tissue samples. Furthermore, the components of the clinical triad, although useful, are not always sufficient since they are not pathognomonic to NPH. Thirty-five percent (35%) of people over 70 have dementia from any cause, 40% of women and 20% of men over 60 have urinary incontinence from another cause, and 20% of people over 70 have some type of gait impediment [9].

To date, the only effective treatment for NPH is a CSF shunting procedure, typically ventriculo-peritoneal shunt (VPS) or ventriculo-atrial shunt (VAS) and sometimes, lumbo-peritoneal shunt (LPS), with a success rate that ranges between 60 and 80%. Hence the importance of appropriate diagnosis and adequate selection of patients for surgery.

3. Pathophysiology

The Monro-Kellie doctrine describes the relationship between the contents of the cranium and intracranial pressure (ICP). The doctrine dictates that the adult cranial vault is a rigid, non-expansible container inside of which there is constant balance of blood, CSF, and brain tissue. If one of the components increases, one of the others or both must decrease, or vice versa, to keep the ICP within the normal range (5–15 mm Hg). This system of homeostasis in the CNS is known as autoregulation. Although the brain is viscoelastic and can change shape and volume after mechanical stimuli, it is the blood and CSF that determine this balance. If one

of the components increases in a progressive fashion, and overcomes the autoregulatory mechanisms, a point of no return or decompensation is reached with an increase in central venous pressure (CVP) and an exponential increase in ICP. When this happens, cerebral perfusion pressure (CPP), which is the difference between mean arterial pressure (MAP) and ICP (CPP = MAP-ICP) decreases, causing brain edema. If this is not corrected, intracranial hypertension (ICH) invariably ensues. It is considered pathologic when ICP levels are more than 30 mm Hg, and life-threatening if more than 40 mm Hg. [10]. CVP is therefore essential in the pathophysiology of ICH.

CSF is the electrochemical medium that provides the appropriate conditions for neuronal metabolism, in addition, since the CNS is immersed, its net weight is ~20–30 g, considerably reducing the risk of mechanical damage [9]. Eighty to ninety percent (80–90%) of CSF is produced in the choroid plexuses of the four cerebral ventricles, richly vascularized epithelial structures whose epithelium constitutes the blood-cerebrospinal fluid brain barrier (BCSFBB) [11]. The remaining 10–20% is produced in the extra-choroidal blood–brain barrier (BBB). Starling's laws (hydrostatic and oncotic pressure gradients), as well as the ionic concentration within the medium are probably the main mechanisms responsible for production, although the exact mechanism is still unknown [11]. CSF flows from the lateral ventricles through the foramen of Monro to the third ventricle, from there through the cerebral aqueduct or Sylvian aqueduct in a pulsatile manner, closely related to heartbeat and respiratory rate, to the fourth ventricle. From the fourth ventricle it passes through the medial opening of Magendie and lateral foramina of Luschka to the subarachnoid space (SAS) and flows upward bathing the tentorium towards the venous sinuses. A smaller amount of volume flows down the spinal SAS. Production is constant and so is reabsorption. Classically it has been said that CSF reabsorption occurs in arachnoid granulations and villi, fenestrated endothelial structures that protrude macroscopically and microscopically, respectively, towards the lumen of the venous sinuses, especially the superior sagittal sinus. It is collectively accepted that retrograde flow from arachnoid granulations is impossible. Some authors point out that almost a third of the CSF leaves the neural sheaths of the cranial nerves to enter the glymphatic system [11]. Therefore, the exact mechanism of reabsorption also remains to be elucidated.

ICP gradients cancel as long as there is constant CSF flow and thus there is no risk of brain herniation. Important concept because when there are abrupt changes in pressure gradients as happens in traumatic brain injury (TBI) or space-occupying lesions, the critical threshold is 20–25 mm Hg, whereas pressure-volume studies in patients with communicating hydrocephalus indicate that these patients tolerate values of ICP in the range of 40–50 mm Hg without symptoms of ICH [12](7). Now, the fact that NPH patients have ventriculomegaly and symptomatic hydrocephalus, but normal ICP is what constitutes the same clinical problem and paradoxical situation that interested S. Hakim and still eludes us today. However, it is important to highlight that some patients with NPH may have episodes of elevated ICP, especially in the early stages of the disease. This phenomenon was explained by S. Hakim based on Laplace's law that explains the behavior of a spherical elastic container containing fluid. The pressure of the fluid inside the container (P) is directly proportional to the elastic tension of its wall (T) and is inversely proportional to the radius (r) of the container [12]:

$$P = 2T/r \tag{1}$$

S. Hakim used the analogy of rubber balloons. As one inflates a balloon, initial pressure is higher than final pressure, as air volume inside the balloon increases, less

pressure is required to be able to introduce more air. Therefore, due to the visco-elastic properties of the brain, as the size of the ventricles (the rubber balloon) increases, pressure required to stretch them decreases. In other words, the pressure inside the container increases until, after a certain stretch point, pressure drops with a subsequent increase in size independent of the wall tension. CSF pressure exerts greater force on the wall of dilated ventricles than in normal sized ventricles. Clarifying this concept, CSF pressure is the necessary pressure to prevent fluid from escaping through a needle that enters the SAS or the ventricle and represents the force per unit of ventricular surface area and/or subarachnoid surface. This is Pascals' law: the total force exerted (F) on the brain would be the result of the multiplication of the pressure (P) and the surface area of ventricular walls (A) subjected to the fluid pressure inside [2]:

$$F = P \text{ x } A \tag{2}$$

Hence,

$$P = F/A \tag{3}$$

To illustrate this, imagine that ICP (CSF pressure) is 150 mm H2O. This means that each squared millimeter of ventricular surface is subjected to the weight of a 150-mm column of water. Now imagine two ventricles of different sizes subjected to the same pressure:

Ventricle A (Av) with a surface area of 20 cm^2 and ventricle B (Bv) with a surface area of 40 cm^2. The force exerted on Av (FAv) is different from Bv (FBv).

$$FAv = 150 \text{ x } 20 \tag{4}$$

Whereas, in Bv:

$$FBv = 150 \text{ x } 40 \tag{5}$$

Thus, we now understand why pressure in both ventricles is the same, but the force exerted on the ventricular wall has increased in relation to the proportional increase in its surface area. Hakim called this phenomenon the *hydraulic press effect*. Of course, this analogy could be criticized, because the visco-elastic properties of the brain also depend on other variables, but due to its mathematical simplicity, it is pertinent [2].

Imbalance between CSF production and reabsorption is the cause of progressive ventriculomegaly. The reason why there is functional obstruction to CSF reabsorption is currently unknown. It must be an alteration in hydrodynamics. CSF reabsorption (Re), which is linear and unidirectional, depends on the gradient between the subarachnoid ICP (ICP_{SA}) and sagittal venous sinus pressure (P_{SS}), a constant parameter that depends on CVP, and is inversely proportional to CSF outflow resistance into the venous space (R_{CSF}), sometimes referred to as *Rout* calculated experimentally at 6–10 mm Hg mL-1 min^{-1} [12]:

$$Re = ICP_{SA} - P_{SS}/R_{CSF} \tag{6}$$

Venous compliance is the ability of veins to distend when intravascular volume and transmural pressure increases against tendency to return to the original dimensions on application of the distending force. In mechanics, it is the inverse of stiffness and the reciprocal of elastance or *coefficient of elasticity*. The increase in CSF within the ventricles causes ventricular dilation and mechanical stretching of the

periventricular white matter, altering viscoelastic properties of the brain, compromising the Windkessel effect, widely studied in systemic circulation but its role in the CNS is also recognized. Mechanical stretching generates intraparenchymal capillary compression which eventually leads to ischemia of *watershed* areas in the territory of the anterior cerebral artery, which reasonably explains the symptoms of the clinical triad. Therefore, one of the most accepted theories about NPH etiology is decreased cortical venous compliance that increases R_{CSF} accompanied by chronic ischemia. This is the reason why if CSF pressure is reduced to subnormal levels after lumbar puncture (LP), venous pressure returns to normal and pushes the dilated ventricles back to their normal position, reversing hydrocephalus. Some authors have reported that $R_{CSF} > 12$ mm/Hg/mL/min is a suitable threshold for predicting responsiveness after surgery [13]. Parallelly, a rise of 3–4 mm Hg in P_{SS} can halt CSF absorption via the arachnoid granulations [14]. Experimental studies in hydrocephalus-induced animal models and prospective clinical studies are needed to elucidate the reasons why cortical venous compliance decreases and why R_{CSF} increases in NPH patients.

Chronic hypoperfusion have shown to cause progressive loss of compliance as well as astrogliosis and neuroinflammation. In fact, glial fibrillar acidic protein (GFAP), a marker of astrocyte axon reactivity and damage is increased in brain biopsy specimens of NPH patients. Additionally, astrogliosis further worsens parenchymal stiffness and contributes to decreased CSF hydrodynamics [15, 16]. Furthermore, NPH patients have significantly more blood–brain barrier (BBB) disruptions than controls which have shown to play a key role in neurologic dysfunction by allowing leakage and entry of blood-borne products into the CNS [17, 18]. BBB disruption and leakage are associated with greater astrogliosis [19].

The recently discovered glymphatic system, which presumably participates to a certain extent in CSF reabsorption, is mediated by aquaporin-4 (AQP4) channels on astrocytic perivascular pedicles [20]. Normal glymphatic system functioning depends on appropriate arterial pulsation, intact AQP4 and healthy sleep pattern [20]. NPH patients have a delayed removal of intrathecal tracers in phase-contrast imaging studies which suggests impaired functioning of the glymphatic system [21, 22]. Decreased AQP4 channel density in perivascular endfeet of NPH patients have also been reported. And it is not unusual that elderly patients suffer from concomitant sleep disorders that might contribute to the pathogenesis [23–27].

4. Etiology and classification

Hydrocephalus is a syndrome caused by a heterogeneous group of pathologies that share an increase in intracranial CSF volume manifested by ventriculomegaly and compatible symptoms. They can be classified as congenital or secondary (acquired), non-communicating or communicating, adult or childhood onset and with ICH or normal pressure. NPH is an acquired type of chronic communicating hydrocephalus with normal ICP whose etiology is still unknown.

NPH could be part of aging process and senescence of the venous endothelium and loss of brain viscoelastic properties, but it has not been possible to determine whether it is related to cerebrovascular and/or cardiovascular risk factors, since not all patients with NPH have a cardiocerebrovascular comorbidity. It could be a degenerative process secondary to the deposit of specific material such as beta-amyloid, something similar to what happens in AD, but its causal relationship has not been determined since not all patients with NPH have neurodegenerative comorbidity. The etiology of NPH still remains unknown for neurologists, neurosurgeons, and neurophysiologists. Thus, is known as idiopathic hydrocephalus.

5. Clinical manifestations

Unlike other types of hydrocephalus, neurologic exam of patients with NPH, except for the clinical triad and minor neurologic signs, is essentially normal. Important, because any sign that suggests focal deficit must make the clinician suspicious of other disorders. Paresis, hyperreflexia, and other first motor neuron signs are atypical. NPH should be suspected in adults with any of the three components of Hakim's triad, but it is not necessary for all three to be present to diagnose NPH. Of the triad components, typically the first one to appear, most frequently encountered and most severe is symmetric apraxia or magnetic gait not explained by another cause and for this reason some authors have called it the cardinal symptom [1]. It is also the first to resolve after surgery in patients with more than one component. Most reports agree that the triad is complete in approximately 60% of cases [28–30]. Nevertheless, a large-scale questionnaire conducted in Japan in 2012 revealed that only 12.1% of a cohort of 1524 patients had the full triad [31].

When all three components are present, the odds of NPH are higher. When there is cognitive impairment, it is important that the patient is accompanied by a family member, preferably his partner or one who lives with the patient to build a medical history and reach the correct clinical diagnosis. After detailed questioning, it has been confirmed that most patients have insidious onset of symptoms within a period of 3–6 months [1]. It is essential to inquire about past medical history, especially cranial surgery or intracranial bleeding, trauma, infection, or CNS tumors, since many of these patients are at risk of secondary hydrocephalus. In patients with ventriculomegaly who only have cognitive impairment or only have urinary incontinence, different diseases should be suspected.

Polyneuropathy is common in the elderly and is a frequent cause of urinary and motor comorbidity. Patients with gait impairment and incontinence without cognitive impairment should be studied for spinal lesions such as cervical or lumbosacral myelopathy secondary to cervical/lumbosacral canal stenosis or discovertebral disease at any level [1].

5.1 Gait

It is the most prominent and frequent (94–100% of patients) [32]. Magnetic gait or gait apraxia is symmetrical, otherwise it suggests other pathologies. Patients drag their feet, as if they are attached to the ground (hence, the term magnetic), the movement is clumsy and hasty, it is accompanied by small steps, frequent stumbling, falls and fear. Walking becomes unstable and slow. Difficulty standing and starting movement is characteristic, as well as erratic turns with many unstable steps, like a compass. Severity is variable and it is sometimes difficult to distinguish between parkinsonism and other dementias such as Lewy's. Unlike in Parkinson's disease, external triggers such as command lines and landmarks have little effect on improving gait [33].

5.2 Cognitive impairment

Cognitive decline in NPH is remarkably similar to that seen in other types of dementia. It includes infantile behaviors, mood fluctuations, amnesia, difficulty managing finances, taking medications, driving, and honoring commitments. Patient denial is common. Psychomotor speed is markedly declined, there is also evident attention and working memory impairment as well as diminished verbal fluency and dysexecutive syndrome [34, 35].

5.3 Incontinence

Urgency and frequency are the most common symptoms, initially without incontinence which appears progressively [36]. Amongst patients with NPH, 90.9% experience dribbling and 75% have incontinence [37]. They mostly are aware of this problem which causes great frustration. A patient with incontinence who is indifferent or unaware is unusual and should raise suspicion of another disorder. All this information is obtained from the patient's companion, usually his/her partner.

5.4 Other symptoms

There are other less frequent manifestations, which traditionally are not listed under NPH manifestations, therefore not commonly searched for, and not treated. An important example is hearing loss. Hypoacusis is present in a non-negligible number of patients with any type of chronic hydrocephalus. Thirty-four percent (34%) of patients who develop post-infectious hydrocephalus and a percentage that can range from 5 to 15% of patients with NPH have some degree of hypoacusis. Its mechanism is not well understood, but it could be secondary to hydrops of the endolymphatic and perilymphatic space, which is continuous with the SAS in the cochlear aqueduct in the posterior aspect of the petrous portion of the temporal bone [38]. In patients with NPH and hypoacusis, significant improvement has been observed after surgery [38]. Possibly if the problem is actively sought and specialized rehabilitation is offered, the outcome could improve significantly.

Approximately, 55% of NPH patients have bradykinesia, 84% have a snout reflex, 77% have an eyebrow reflex and 65% have some degree of paratonia [39]. In a study that compared patients with NPH, Parkinson's and healthy controls, the NPH group had decreased speed when lifting things and used more strength to grip compared to healthy controls. This correlates with involuntary motor dysfunction which resembles frequent neurologic deficit seen in Parkinson's.

5.5 Symptom assessment

The most important thing is to detect the components of the triad and to explore their characteristics in depth. As mentioned previously, other diseases should be ruled out [1].

When clinical suspicion is high, some important domains such as motor and cognitive performance should be evaluated profoundly. Different formal tests have been developed that allow objective and quantitative measures of compromise in all domains. We summarize tests that have been validated and recommended by clinical practice guidelines. Those tests are used in our NPH center of excellence (COE) at Fundación Santa Fe de Bogotá (FSFB), the only COE of its kind in Colombia currently accredited by Joint Commission International (JCI).

5.5.1 Gait

- Timed-up and go test: Time the patient takes to stand from the seat, walk 2 meters, turn 180°, walk back and sit down. This test has proved to be cost-effective, with high sensitivity, specificity, and positive predictive value (PPV) for favorable outcome after surgery [40].

- 10-meter test: Time the patient takes to walk 10 meters in a straight line starting in a standing position. Evaluation time is between meters 2 and 8 to minimize the effects of acceleration and deceleration [41].

- Tinetti: Test that integrates gait and balance with a maximum possible score of 30. The higher the score, the better motor performance. It has proven useful in evaluating response in patients undergoing CSF shunting surgery [42].

5.5.2 Cognitive decline

- Mini-Mental State Examination (MMSE): Widely known test that assesses various mental domains in 30 items including memory, praxis, literacy, and mathematical abstraction. Scores ≤23–25 suggest cognitive impairment and this score can be compared in the postoperative period with high specificity [40]. This type of test, although used for screening, is particularly useful in NPH patients with significant cognitive impairment.

- INECO frontal screening (IFS): Assesses executive processes that include motor response programming, inhibition of both motor and verbal responses, abstraction, verbal, and special working memory; also evaluates frontal dysfunction. The maximum score is 30 [43].

5.5.3 Incontinence

- ICIQ-SF (international consultation on incontinence questionnaire-short form): Validated questionnaire addressed to the patient and his/her companion evaluating frequency, severity, and impact of incontinence on the patient's quality of life. Score is 0–21, the higher the result, the more symptoms and the greater the negative impact on quality of life. There is a significant decrease in ICIQ-SF mean score after CSF shunting surgery [42].

5.5.4 Others

- FIM (functional independence measurement): Measures disability and level of dependence on another person in motor and cognitive domains that has shown high reliability [44].

- Zarit survey: Validated questionnaire to assess the degree of caregiver burden. It is done before and after surgery at each follow-up visit. The SINPHONI study demonstrated that the degree of caregiver burden decreased markedly after the patient's surgery and correlated with improvement in Hakim's triad symptoms [42].

6. Diagnostic tests

Despite the immense amount of research on NPH, to date, there is no gold standard test for its diagnosis. Therefore, diagnosing NPH is a challenging task that results from gathering information on clinical manifestations, radiographic findings, clinical response after tap test, and recently, certain CSF biomarkers.

6.1 Imaging

After the aforementioned tests, a CNS image is necessary. Of choice, brain magnetic resonance imaging (MRI) or computed tomography (CT) if MRI is contraindicated or not feasible; MRI is preferred due to its higher resolution and definition of parenchymal structures whether healthy or pathological.

According to the Japanese Guidelines for management of Idiopathic Normal Pressure Hydrocephalus, the imaging findings that suggest NPH are: ventriculomegaly not attributable to other pathology, disproportionately enlarged subarachnoid space hydrocephalus (DESH), acute callosal angle and posterior narrowing of the cingulate sulcus seen on sagittal plane MRI [32].

The main finding is ventriculomegaly assessed with the Evans' Index (EI), which is calculated by measuring the maximum width of both frontal horns of the lateral ventricles and dividing it by the maximum intracranial width in the same slice of axial plane; a normal value is <0.3 (**Figure 1a**). A newly proposed z-Evans' Index has shown an increased diagnostic value, it is measured in the coronal plane and is a ratio of the maximum frontal horn height and the vertical diameter of the skull at the midline, the normal value is <0.42 (**Figure 1b**) [45, 46]. The distribution of subarachnoid spaces changes with NPH as well as neurodegenerative diseases such as AD and Parkinson's disease. A characteristic pattern that aids in differentiating NPH from other pathologies is DESH, its imaging features are narrowed subarachnoid spaces of the midline and high convexity with dilation of the Sylvian fissures, associated with ventriculomegaly (**Figure 1c**). In contrast,

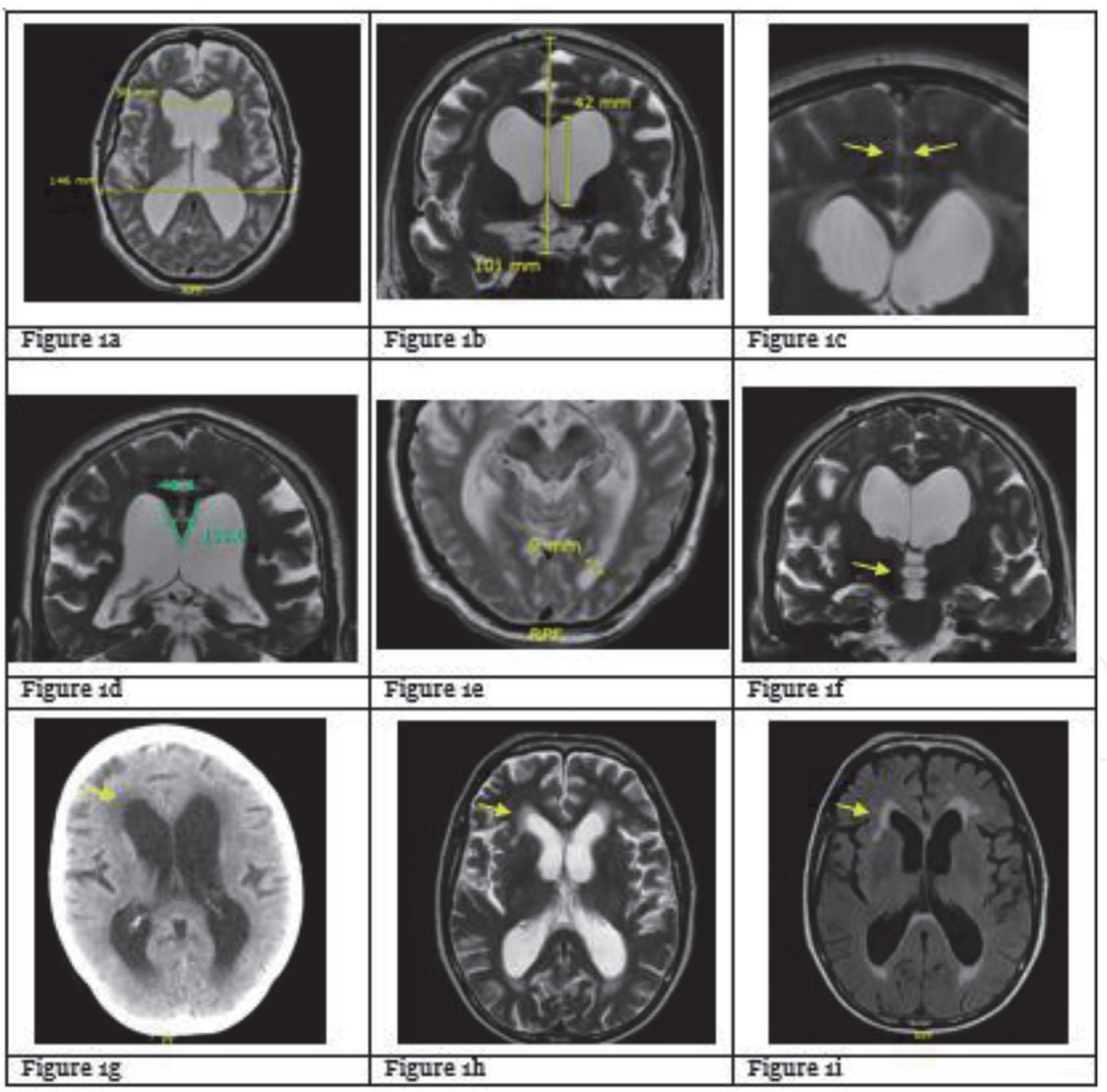


Figure 1.
NPH imaging findings. a. T2WI axial MRI. Evans' index b. T2WI coronal MRI. Z-Evans' index c. T2WI coronal MRI. DESH d. T2WI coronal MRI. Callosal angle e. T2WI axial MRI. Temporal horns f. T2W1 coronal MRI. Ventricle ballooning g. axial CT. Transependymal CSF flow h. T2WI axial MRI. Transependymal CSF flow i. T2WI Flair. Transependymal CSF flow. Images obtained from FSFB NPH COE database.

generalized widened sulci with ventriculomegaly is seen on neurodegenerative cerebral atrophy [47]. Due to morphological changes attributed to DESH, vertical distortion of the lateral ventricles is more commonly associated with NPH and is evidenced in the CA, which is the angle formed by the right and left parts of the corpus callosum and is measured in a plane perpendicular to the anterior commissure-posterior commissure plane (AC-PC) through the posterior commissure; patients with NPH have an acute angle (<90°) whereas healthy patients or patients suffering from other diseases have an angle >90° (**Figure 1d**). Proper alignment of the true perpendicular plane must be achieved to avoid over or underestimation of the CA [48]. A systematic review conducted by Park et al. analyzed the diagnostic performance of the EI and CA and demonstrated that the CA yields a higher diagnostic value than EI (CA: 91% sensitivity and 93% specificity versus EI: 96% sensitivity and 83% specificity) [49].

A less common method is to measure the thickness of both temporal horns of the lateral ventricles in an axial section and if this value is >2 mm it is highly suggestive of ventriculomegaly (**Figure 1e**). Lateral ventricle ballooning and/or slit-shaped third ventricle also suggest ventriculomegaly (**Figure 1f**). In cases of third and fourth ventricular dilation, it is important to rule out triventricular or tetraventricular hydrocephalus due to mechanical obstruction of another cause [50]. Other signs are low periventricular density on CT or hyperintensity on T2WI or FLAIR MRI sequences immediately adjacent to the ventricular wall, which is highly suggestive of transependymal flow of CSF (indirect sign of hydrocephalus) (**Figure 1g–i**). More peripheral white matter lesions, such as those in corona radiata, suggest ischemic changes [50]. It is important to differentiate ventriculomegaly in NPH from compensatory *ex vacuo* ventriculomegaly secondary to atrophy, typical of other diseases. Focal atrophy indicates other types of dementia, especially if it is asymmetric, as in FTD or hippocampal atrophy in AD.

There are MRI techniques that analyze the movement of CSF and water that offer further insight about the pathophysiology of NPH. One is phase contrast MRI (PC-MRI) which is an invasive technique that measures flow of ejected CSF in specific anatomic regions, especially the cerebral aqueduct. It is based on the pulsatile relationship of CSF flow with heartbeat and respiratory rate and known relaxation times of CSF in T1WI and T2WI sequences with respect to static tissue. Limitations include that it is invasive, gathers information from many cardiac cycles, and evaluates only certain regions [51]. Another reported issue in NPH is increased CSF pulsatility. Aqueduct flow is reduced or even absent in phase contrast MRI (PC-MR) [52–54]. Aqueduct stroke volume (ASV), defined as the average of flow volume through the aqueduct during diastole and systole, may be an indirect parameter of CSF pulsatility. Various studies have shown increased ASV in NPH patients compared to healthy controls. Luetmer et al. demonstrated that ASV elevation assists in diagnosis and in differentiating NPH from other dementias. ASV greater or equal to 42 L has been applied to identify patients who might benefit from shunting procedure [55]. Scollato et al. reported that patients with higher ASV may benefit from shunting [56]. Aqueduct pulsatility reflects capillary expansion, mainly influenced by the pulsatile dampening of arteries in the Windkessel *effect* [57, 58].

Time-spatial labeling inversion pulse or *SPLIT*, a non-invasive technique that synchronizes CSF flow with the arterial pulse. SPLIT evaluates both linear and turbulent movement of CSF between two compartments in any anatomic region of the CNS for periods of up to 5 seconds (22). The observed flow patterns are not the same as those classically described, even in brains without hydrocephalus. In fact, retrograde aqueduct flow generates sustained pressure gradients that favor compressive stress and shearing force on the ependyma. The causal relationship

between ASV and ventricular volume has been confirmed [59]. Further improvements in this technology will probably offer valuable information on the pathophysiology of NPH in the short-coming future.

Arterial spin-labeling or ASL-MR perfusion is a non-invasive technique without the need of intravenous contrast administration. Instead, ASL-MR perfusion technique is based on the principle of magnetically labeled water molecules in blood, hence, water in blood entering the CNS is used as an endogenous tracer. Unlabeled images are subtracted from labeled images obtaining a regional blood flow map. Some authors have used ASL-MR to study changes in cerebral flow in patients with NPH and have found a positive correlation with clinical changes before and after surgery [8]. Diffusion tensor imaging (DTI) has gained popularity for the diagnosis of NPH, following dilation of the lateral ventricles comes abnormalities and compression of the surrounding periventricular white matter. The research on the usefulness of DTI in NPH has been focused on its diagnostic value and ability to differentiate NPH from other neurodegenerative diseases, the areas of interest are the corpus callosum, internal capsule, hippocampus and the corticospinal tracts to which gait disturbance could be attributed. Fractional anisotropy (FA) which is a measure of the direction of diffusion, is reported in absolute values ranging from 0 to 1 where 0 means free flow of molecules and 1 means restricted linear flow. Increased FA signal is reported as a prominent characteristic in NPH compared to other neurodegenerative diseases like AD or Parkinson's disease where FA is decreased. However, recent research reports decreased FA of the corticospinal tracts in NPH [60].

Single photon emission computed tomography (SPECT) can be used for analysis of cerebral blood flow (CBF) when studying NPH, the characteristic CBF pattern observed in NPH is known as convexity apparent hyperperfusion (CAPPAH) which consists in increased CBF in midline and convexity with decreased perisylvian perfusion congruent with DESH morphology [32, 46]. Glucose metabolism assessed with Positron Emission Tomography is useful for distinguishing NPH from other pathologies when decreased basal ganglia metabolism is present. MRI flowmetry and spectroscopy have not been shown superior to the aforementioned imaging methods, therefore cannot be recommended [32]. Other nuclear medicine techniques such as dopamine transporter scintigraphy, fluorodeoxyglucose-PET (FDG-PET) and amyloid-PET have also been studied in NPH offering possible diagnostic aids.

Given the interobserver variation in the findings on brain imaging suggesting NPH, an objective standardized guideline or scale would be warranted. A radiologic scale (iNPH Radscale) was proposed in 2017 by Kockum et al., evaluating the correlation of NPH symptoms and seven radiological findings in CT: EI, CA, DESH (Sylvian fissure dilation and narrowing of parafalcine or high convexity sulci), temporal horn enlargement, focal enlargement of sulci and periventricular hypodensities, with a score ranging from 0 to 12. The study results showed that a higher score was related with a higher symptom burden, however the cohorts studied were only from a Swedish town [61]. In 2020 the diagnostic performance of the iNPH Radscale was evaluated by its author, the follow-up results showed that a cutoff value of 4 had high diagnostic value with a sensitivity of 100% and specificity of 96%, which could be a useful diagnostic tool in the future when further studies are conducted with regards of its diagnostic values in other populations [62].

6.2 Tap test

One of S. Hakim's most important lesson is that lumbar puncture (LP) is a technically simple procedure, with roughly null complication rate and cost-effective that provides valuable information on neurophysiology. Tap test simulates a

drainage device improving NPH symptoms. However, it has a low sensitivity and there is no consensus on the parameters that should be used nor the volume to be extracted. In our NPH COE at FSFB, all suspicious cases of NPH undergo a modified tap test that consists in a conventional LP: the patient is in a lateral decubitus position and an 18-gauge (18.0 Ga) spinal needle is used. The amount of CSF obtained is determined by reaching a closing pressure of 0 cm H_2O regardless of the volume, thus there is no fixed volume to extract. We recently carried out a descriptive cross-sectional study in which 92 patients with a mean age of 79.4 years were included. The diagnosis was confirmed in 73.9% of cases (validity comparable to that reported in the literature). The mean opening pressure was 14.4 cm H2O and the mean volume extracted was 43.4 mL [63]. These results warrant further trials to determine if this modified tap test could eventually become the gold standard. If opening pressure is normal and there is objective improvement in symptoms and formal tests 24 hours after LP, the patient is considered candidate for CSF shunting surgery.

6.3 Lab tests

Although most patients have one or more symptoms of the clinical triad, as well as typical findings in imaging, and procedures that can lean towards the diagnosis of NPH, no gold standard has been established. For this reason, since 1990 some authors have studied the role of biomarkers in serum and CSF that had not been frequently used before despite their proved diagnostic value in other neurodegenerative disorders, especially AD. Results using serum biomarkers were not promising, and the authors concluded that as long as the BBB is intact, as it would be expected in NPH, serum levels of those markers would not have diagnostic utility [64–66].

To date, there is no consensus on the biochemical profile of NPH and the differences with the profile of some neurodegenerative disorders, but interesting data has been obtained on some biomarkers:

Amongst neurotransmitters, activity of AChE in CSF has been positively correlated with MMSE scores in patients with NPH and AD, which is reduced in these diseases [67–69]. Other neurotransmitters have not been proven to be useful due to their ubiquity in the CNS and poor correlation.

Somatostatin (SOM) levels have been described as lower in NPH patients compared to controls and these levels have increased after CSF shunting surgery. Increase in SOM levels correlates positively with cognitive performance (memory and visuo-motor) after surgery, but this does not persist over time [70, 71]. Neuropeptide Y (NPY) levels are also reduced in NPH compared to controls and increase after surgery, although they are also low in patients with AD, so this finding is not specific of NPH [71, 72]. Vasoactive intestinal peptide (VIP) is markedly elevated in patients with SAD or Binswanger's disease and in general in vascular dementias. VIP levels are higher in patients with NPH and cerebrovascular comorbidity compared to a NPH group without any comorbidities [73].

Tumor necrosis factor alpha (TNF-alpha) levels may be increased up to 45-fold above reference range in NPH patients and interestingly, TNF-alpha levels normalize after surgery, suggesting a pro-inflammatory component not yet studied in NPH. Its half-life is short and therefore researchers highlight it is not related to stagnant CSF or siphoning effect after implantation of the shunting device. It could be a specific marker with a high PPV [74]. Vascular endothelial growth factor (VEGF) is a proangiogenic cytokine that serves as a marker for chronic hypoxia. Its levels are elevated in patients with NPH compared to controls; the higher VEGF levels, less response to surgery and worse clinical outcome [75, 76].

Myelin basic protein (MBP) is a reliable marker of demyelination, and hydrocephalus is known to cause periventricular demyelination by mechanical stretch, hence, the degree of ventriculomegaly has been positively correlated with MBP levels. Brain atrophy, though, does not raise MBP levels [77, 78]. These levels decrease after surgery, which supports the theory that ventriculomegaly in NPH does not produce atrophy but cerebral pseudoatrophy, studied by some authors including Fernando Hakim et al. and correlates with clinical improvement after surgery [79–83].

In a study of experimentally-induced hydrocephalus in rats, postoperative MBP levels were lower in models operated 1 week after induced hydrocephalus compared to models operated 4 weeks later [84]. This supports the idea that the earlier hydrocephalus is diagnosed and treated, the better the outcome for NPH patients.

Beta-amyloid is a peptide synthesized from amyloid precursor protein (APP) whose biologic functions include enzymatic co-factor, cholesterol transport, and pro-inflammatory activity. The diagnostic role of beta-amyloid deposits in AD has been largely studied. Especially the ratio of its isoforms (AB42 / AB40) which has a higher diagnostic value than AB42 alone. The levels of AB42 and AB40 isoforms are low in NPH compared to AD [84, 85]. They could be helpful in distinguishing between NPH and AD. Nearly half of NPH patients show certain degree of amyloid deposition in brain biopsy specimens while only 10% show concomitant amyloid and tau pathology [86]. Tau is a protein of neural tissue microtubules and serves as a marker of neuronal degeneration in other types of dementia like AD, Lewy's, corticobasal degeneration, and prion disease (Creutzfeldt-Jakob). The levels of total tau (t-tau) and phosphorylated tau (p-tau) have been positively correlated with the severity of dementia in AD, as well as with cognitive decline and urinary incontinence in NPH, although they are lower in NPH compared to AD [84, 87]. Neurogranin (NRGN) has also been studied in AD patients and has been associated with amyloid plaques [88, 89].

Neural growth factor (NGF) mRNA levels are elevated in the basal nuclei of experimentally-induced hydrocephalus models, this is why they could act as markers of early neuronal injury that stimulates glial recruitment [90]. Neurofilament light chain (NFL) is increased in NPH, AD, and other dementias, but there is no correlation with clinical manifestations, severity, or response to surgery. A Swedish study reported 100% PPV for positive outcome after surgery, with 17% sensitivity and 100% specificity [91, 92]. It could be a marker of ongoing axonal damage.

Sulfatide is a glycosphingolipid component of myelin. Its levels are higher in NPH and cerebrovascular comorbidity, but no correlation with postoperative outcome has been reported. According to one study, sulfatide differentiates NPH from SAD with 74% sensitivity and 94% specificity [93]. Glial fibrillary acid protein (GFAP) and S-100 are markers used in tumor immunohistochemistry that have not shown conclusive data in NPH.

Recently, the first longitudinal comparison of CSF biomarkers in NPH patients and AD was conducted by a group in Finland. Furthermore, they compared the gradients of biomarker concentrations lumbar and ventricular CSF which are discordant. All markers increased notably by 140–810% in lumbar CSF, except beta amyloid that had an erratic behavior. All studied biomarkers (tau, NFL, NRGN and beta amyloid) correlated highly between lumbar and ventricular samples but were systematically lower in ventricular samples [94]. Longitudinal follow-up shoed that after initial postoperative increase, tau and NRGN levels are stable in NPH regardless of brain biopsy amyloid pathology. NFL normalized after surgery to pre-shunting levels. Amyloid is the less affected by shunting and may be the best predictor of concomitant AD risk in NPH patients [94]. Tau levels (both p-tau and

t-tau) have shown a steady increase of 2% per year in AD [95]. In cases of TBI, t-tau levels increase but normalize to baseline levels by day 20–43 post trauma [96, 97]. This is different, however, for patients who suffer chronic TBI like boxers, for example [97]. Interestingly, NFL levels after surgery correlated with tau and NRGN, raising the question if their increase is related to disease process or the shunting procedure itself. Future larger randomized trials are warranted to elucidate the role of CSF biomarkers in NPH progression, surgical prognosis, and risk of concomitant neurodegenerative disorders.

7. Brief history of CSF shunting devices

The main principle is shunting CSF to another sterile cavity with constant flow and/or where fluid can be reabsorbed to the systemic circulation. The quest for an effective system is not recent. Le Cat performed the first documented ventricular puncture in 1744 [98, 99]. Throughout the XIX and XX centuries, different devices were designed as well as different shunting techniques that included ventriculo-subarachnoid-subgaleal, lumbo-peritoneal, ventriculo-peritoneal, venous, pleural, and uretheral. All failed in the short-term because implant materials that included glass, rubber and guttapercha were not adequate and aseptic techniques were extremely poor with high rates of infection [99]. There were also cases of sudden death before the advent of appropriate imaging techniques which fortunately decreased after Dandy introduced the pneumo-ventriculography in 1918. Pneumo-ventriculography remained the gold standard until 1980 when Humphrey introduced the computed tomography [99]. During the first half of the XX century different techniques were proposed such as choroid plexus cauterization and draining systems to intra and extracranial veins. Infection and material rejection were the main causes of failure. Developing a biocompatible unidirectional system was paramount.

Torkildsen described the ventriculo-cysternostomy in 1938 in a case of spontaneous cure of hydrocephalus after an accidental rupture of the fourth ventricle during surgery. This became a popular method to treat obstructive hydrocephalus until the early 1970's [100]. Vannevar Bush engineering professor at Massachussets Institute of Technology (MIT) and Donald Matson, surgeon at Harvard Children's Hospital were possibly the first to develop a magnetically-operated valve by 1950. Although there is no certainty on the exact date of implantation, around 18 devices were implanted by 1957 but this project was soon abandoned because results were not promising [99]. Ommaya invented the subcutaneous reservoir in 1963, his device is still today the method of choice for obstructive hydrocephalus in children with minor modifications to the original design [101].

7.1 First effective devices

The long-sought biocompatible material is silicone, an inorganic polymer derived from polysiloxane (series of oxygen and silicon atoms) whose properties include inert, malleable, resistant to high temperatures and stretching. Silicone has its origins in World War II, like many other inventions, because materials that resisted high temperatures, provided electrical insulation, and resisted mechanical stress for aircraft construction were urgently needed. In 1946, a silicone tube was implanted to repair a bile duct. In 1956, it was used as a CSF drainage device by Holter and Pudenz and thus became the ideal material for different valve designs [99]. However, these devices failed because, due the mechanism of the opening slit when CSF pressure increased, they were imprecise.

In 1964, S. Hakim introduced his first valve that consisted of two twin valved systems made of stainless steel and synthetic sapphire manufactured by himself in his home lab. It was one of the first precise models that controlled pressure [102]. By 1965, S. Hakim had published his observations in the NEJM and NPH or Hakim's syndrome was recognized as a separate entity by the scientific community. A second generation of devices intended to solve the problem of overdrainage in the upright position. Kuffer and Strub designed a piston-based system in 1969, but it never became popular and the same happened with some successive designs. S. Hakim introduced a valve that could be operated magnetically and percutaneously in 1973 [99]. In that same year, he introduced a self-regulating device, nonetheless, the first patented self-regulating valve was that of Sainte-Rose in 1984 (Cordis Orbis-Sigma). Portnoy later designed his *anti-siphon* device patented by Schulte in 1973 (Heyer-Schulte ASD). This is a flapping membrane mechanism that closes progressively when subjected to the weight of a hydrostatic column in the distal catheter. These mechanisms failed because they were highly susceptible to external tissue pressure. In 1975, S. Hakim patented the first *anti-gravitational* device [99].

At the time, S. Hakim's oldest son, Carlos, was already a mechanical engineer starting his post-doctoral fellowship at MIT in biomedical engineering. Carlos studied hydrocephalus in animal models. In his thesis he questioned some aspects of his father's original theory including the concept of brain elasticity. Carlos demonstrated that if the brain were elastic, dilated ventricles would return to normal dimensions after a shunting device was implanted. This does not happen in all cases and it depends on how much time ventricles have been subjected to the *hydraulic press effect*. He introduced the concept of brain *plasticity*. Carlos Hakim also demonstrated that the thin walls of the venous system in an adult human are easily compressible when subjected to high external pressure in the upright position. Thence, demonstrated that the anti-siphon effect was not true. Instead, he associated with Swiss watchmakers who were pioneers in micromechanics and developed the first *programmable* valve with 18 pressure positions ranging from 30 to 200 mm H_2O (Medos-Hakim). This device was first implanted in Colombia by S. Hakim and was approved for commercialization in 1989. It soon demonstrated superiority compared with all other available designs and entered Europe in 1990 [99]. Today, this design is distributed by Johnson & Johnson as the Codman Hakim™ programmable valve which has proved superiority systematically.

By 1999, at least 127 models of different mechanisms were available. Most of them rudimentary unidirectional systems based on pressure gradient with ball and cone (13 models), diaphragm (>35) and slit (>50) [99]. To date, >60 models were never evaluated in lab and 40 were only in tested in one or two specimens, hence, their value is only anecdotal. Compared with other high-tech devices in the biomedical field, like pacemakers, most valves are imprecise, unsafe, obsolete, and cheap. By 2000, the mean cost per device was $600 USD. Assuming a mean device lifespan of 10 years, this equates to 17-dollar cents/day. The total cost of sold devices in the USA by 1995 was 20.8 million dollars which was the equivalent of 8-dollar cents/per capita [99, 103].

8. Surgical treatment

8.1 Surgery

To date, the only effective treatment of NPH is a CSF shunting procedure that involves implantation of a draining system that diverts excess intracranial CSF into a sterile cavity where CSF returns to or is reabsorbed into the systemic circulation.

The system should ideally be a programmable valved device. Shunting techniques include VAS, VPS, LPS, and rarely ventriculo-pleural shunt (VPlS). VAS and VPS are the most commonly used in clinical practice. S. Hakim originally described VAS arguing that it was physiological and of choice at our NPH COE. LPS is very common amongst Japanese surgeons, however, it is technically complex and can have a higher rate of perioperative complications. DVPl is seldom used due to a high complication rate and lower reproducibility. It is consensus that endoscopic third ventriculostomy (ETV) is not effective for treating NPH.

8.1.1 VAS

It is considered the technique of choice. Between 1970 and 1980 it was hardly criticized because it was an expensive technique that required vascular dissection, hence, with multiple complications such as vascular rupture, embolism, and infection. However, with the advent of Seldinger-type techniques guided by ultrasound (US) and constant electrocardiographic monitoring, which do not require vascular dissection, incidence of complications in VAS does not exceed that of VPS [104, 105].

At our NPH COE, VAS is performed in all patients unless contraindicated. The technique consists of puncturing the internal jugular vein (IJV) using a US-guided Seldinger technique and continuous EKG monitoring. A 7-Fr peel-away disposable sheath catheter is used. This allows easy, safe, fast, and reproducible insertion and positioning of the distal catheter in the cavo-atrial junction which is the correct position (guided by fluoroscopy) [105]. Trained surgeons can perform the whole procedure within 30 minutes, with a lower perioperative complication rate than other techniques. Hung et al. reported that patients with NPH undergoing VAS are less likely to develop obstruction and/or require device revision compared to the group undergoing VPS [105]. Serious thromboembolic complications associated with VAS such as in situ thrombus formation, intracardiac thrombi, pulmonary artery thromboembolism and pulmonary hypertension, which have a high morbidity and mortality rate, are uncommon, with an estimated prevalence <1%. Adjuvant therapy with direct anticoagulant agents like rivaroxaban has been proposed, but currently, there is no robust evidence to support such recommendation as a preventive strategy [105–107].

8.1.2 VPS

Became the most popular technique since 1970 because of the vascular complications encountered in VAS. However, there is a non-negligible percentage of patients in whom it is advisable not to use a distal peritoneal catheter due to inflammatory or infectious diseases in the abdominal cavity, as well as a slightly higher incidence of distal obstruction. Patients undergoing VPS, have an estimated incidence of device-related complications in the peritoneal cavity ranging from 5 to 47%, depending on the series. Complications include device infection, pseudo-cyst, adhesion, and malposition (scrotum, bladder, small intestine, and hernia) [108].

8.1.3 LPS

Murtagh was the first to introduce a lumbo-peritoneal catheter through a Touhy needle [83]. Rarely used amongst Western surgeons, but extremely popular amongst Japanese neurosurgeons. Described as a less invasive and effective alternative in high-risk patients in whom the right atrium and peritoneal cavity cannot be used. Significant improvement has been reported in the components of Hakim's

triad, however, the complication rate is 20% [28, 109, 110]. This technique is not routinely recommended unless the surgical staff is highly experienced.

8.1.4 VPlS

An alternative when VAS or VPS are contraindicated, however, the complication rate is high including hydrothorax, pneumonia, and pleural effusion. It is not considered an efficient long-term option [111].

8.1.5 ETV

Described in 1990 as an alternative approach for cases of obstructive hydrocephalus and some selected cases of communicating hydrocephalus, has recently gained attention as an alternative approach that saves device implantation. However, conducted trials have small numbers of patients and lack randomization, therefore its effectiveness and generalizability in NPH is still limited [112, 113].

The thorough description of each surgical technique is beyond the scope of this chapter.

8.2 Prognosis after shunting procedure

Despite variability in evaluation methods, gait disturbance has systematically showed the highest rate of improvement (60–77%). Cognitive decline improves in 60–70% of cases and urinary incontinence improves in 52% of cases [114–118]. Surely, these rates vary according to different diagnostic criteria, evaluation methods and improvement thresholds.

Short-term outcomes are mainly affected by perioperative complications and by severity and duration of disease before treatment. Long-term outcomes strictly depend on other neurologic comorbidities, hence the importance of diagnosis these disorders using biomarkers before and after surgery to help patients and their families conveying their expectations. Frailty and/or comorbidity indices can be helpful for perioperative outcome evaluation.

8.3 Shunt procedure cost-effectiveness

Based on SINPHONI and SINPHONI-2 results, incremental cost-effectiveness ratio 1 year after shunt surgery was 29934–40742 USD/quality-adjusted life year (QALY) for VPS and 58346–80392 USD/QALY for LPS. Additionally, the sum of surgical cost and nursing cost for NPH is reduced to 18 months after VPS and 21 months after LPS, compared with untreated NPH patients [119].

Some authors studied the economic effect of NPH treatments using the Markov model based on epidemiologic data from Sweden. These authors reported that an additional lifetime of 2.2 years and 1.7 QALY was gained with treatment, with an additional cost of 13,000 GBP [120].

8.4 Non-surgical treatment

To date, there are no FDA-approved pharmacological therapies for NPH. Clinical trials suggest that carbonic anhydrase inhibitors (CAIs) such as acetazolamide can reduce periventricular white matter hyperintensities and thence improve NPH symptoms [121]. However, these studies have flawed designs which confound their results and render their conclusions temporarily invalid. Prospective, double-blinded, and placebo-controlled trials are warranted.

Future improvements in technology within the pharmaceutical industry may offer novel supplementary agents that tackle NPH pathogenesis. These drugs could normalize CSF hydrodynamics by tackling CSF production, pulsatility and Rout. They could also restore cerebral blood perfusion and parenchymal compliance as well as promote brain waste products providing neuroprotection and reducing neuroinflammation.

9. Complications after CSF shunting surgery

Main complications include infection, catheter malposition (proximal and distal), and hydraulic device-associated complications. Infections are responsible for 10–15% of device revisions, but their impact on morbidity and mortality is high. The cost of managing a patient with an infected device is approximately $30,000 USD [103]. Most infections are secondary to intraoperative contamination of the implant [99]. Trained surgical staffs that meet strict aseptic techniques and are able to reduce operating time have infection rates <1%. In 3 independent meta-analyses, the use of prophylactic systemic antibiotic decreased infection rate to 5–6% compared to 10–12% in controls without prophylaxis [122–124]. At our NPH COE, intravenous Vancomycin is infused during a 60-minute period before incision.

Catheter malposition, both proximal and distal, is the most common cause of shunt system failure, but it is an unpopular topic in the literature [125]. Probably due to ambiguity in the definition of perioperative complication and the methods used to analyze them. At some point in the post-operative follow-up period, approximately 17% of patients develop complications associated with overdrainage such as hygromas and subdural hematomas, postural headache, slit ventricular syndrome and, occasionally, bone table deformities. Other less frequent ones include proximal occlusion, sequestered ventricle, upright ventricular hyperemia, intraparenchymal or intraventricular hemorrhage and/or partial sometimes irreversible loss of cerebral compliance [126]. Postural headache along with hygromas and laminar subdural hematomas, can be managed with pressure adjustment of the device. According to a recent metanalysis, the need for additional surgery was 9–16% of patients operated with an adjustable device and 26–38% in patients with a fixed-pressure device [127]. These are the main reasons to use programmable devices because percutaneous pressure adjustment saves additional surgical interventions for complications that can be resolved non-invasively. When the hygroma or subdural hematoma is large, it produces intractable headache and/or progressive neurologic deficit, surgery to drain the space-occupying lesion, device revision and proximal catheter relocation is indicated.

Novel shunt catheters manufactured with advanced biomaterials that avoid cell and bacterial adhesion as well as *smart* devices with auto-regulating monitors are underway which promise better treatment outcomes [128].

10. NPH COE protocol

At FSFB, we designed a NPH protocol based on the best available evidence and standards. Our protocol has been certified and accredited by Joint Commission International (JCI). The protocol consists of 5 phases with specific goals to diagnose and treat NPH in an optimal way. The main purpose of this protocol is helping the patient reintegrate to his/her daily activities and community (**Figure 2**).

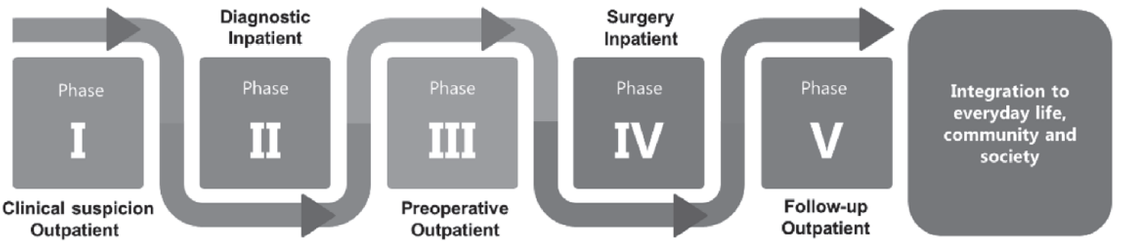


Figure 2.
FSFB NPH COE protocol.

Gait impairment (praxia/symmetric magnetism) or cognitive decline or urinary urgency/incontinence
Radiographic signs suggestive of NPH
Absence of other neurologic disorder that could explain current symptoms

Table 1.
Inclusion criteria. Patients should have at least one of the following (≥ 1).

10.1 Phases

10.1.1 Phase 1 (clinical suspicion)

Patients either consult or are referred because have signs and symptoms suggestive of NPH. The objective of this phase is to identify suspicious cases. Patients undergo a complete neurologic examination and interview by one neurosurgeon of our team. The physician orders a brain MRI or CT scan whenever MRI is contraindicated. Suspicious cases are those who meet the inclusion criteria listed in **Table 1**.

10.1.2 Phase 2 (diagnostic tests)

Patients who met the inclusion criteria and consent are admitted for a 2-day inpatient analysis. The patient undergoes thorough evaluation by neuropsychology, speech and language therapy, rehabilitation medicine and geriatrics specialist using all diagnostic tests that have been mentioned before. In all patients >64 years, an elder adult frailty test is performed. Depending on each individual case, social work and nutrition specialist may also be involved. Then we perform the modified tap test we described above by taking the system to a closing pressure of 0 cm H2O. All tests are repeated 24 hours after tap test. Tests performed before and after tap test are listed in **Table 2**. Thereafter, the patient is discharged and followed during 7 days via phone call to inquire on symptom improvement.

After this week of follow-up, a multidisciplinary team consisting of all neurosurgeons, psychology, speech and language therapy, rehabilitation medicine and geriatrics meets to analyze objective changes in all tests before and after tap test. Diagnosis is confirmed when patients objectively improve in at least 1 of the triad components. Diagnostic criteria are listed in **Table 3**. Once the diagnosis of NPH is confirmed, the team decides if the patient benefits or not of a CSF shunting surgery. When NPH is discarded, patients are referred to the required specialty.

Patient companions undergo the Zarit caregiver's burden test before and after tap test to evaluate the degree of burden/fatigue.

10.1.3 Phase 3 (preoperative assessment)

If patient and family agree with the team's decision, the patient undergoes regular preoperative tests, anesthetic evaluation, and an institutional risk mitigation

Area	Test
Physical rehabilitation	FIM
Physical therapy	Tinetti assessment tool
Occupational therapy	• MMSE • Pegboard test
Neurosurgery	Gait: • Timed-up and go. • 10-meter test Incontinence: • ICIQ-SF Burden: Zarit
Neuropsychology	• IFS • Stroop's color test • CERAD/ADAS-COG • Rey-Osterrith's complex figure

Table 2.
Tests performed before and after tap test.

Time ratio between any gait test before (t1) and after (t2) tap test greater than 1: t1/t2 > 1
Subjective improvement in gait symptoms after tap test according to specialist
Objective improvement after tap test in at least one neuropsychological test
Objective improvement in FIM scale
Subjective improvement after tap test according to patient companions
Objective improvement in ICIQ-SF score after tap test
Normal CSF pressure during tap test
At least one of the following: EI > 0.3, periventricular transependimary flow and/or convexity tightness

Table 3.
Diagnostic criteria at FSFB NPH COE.

form. Patients are then scheduled for CSF shunting. Patients and family receive rigorous education on the procedure and postoperative care.

10.1.4 Phase 4 (surgery)

Patients are admitted for VAS or VPS when VAS is contraindicated.
All cases include:

- Prophylactic IV vancomycin one hour before incision. If allergy to vancomycin is present, clindamycin is used.

- All patients are operated using a programmable device.

- The technique of choice is a Seldinger-type US-guided VAS using a peel-away 7-Fr disposable catheter. Correct position is confirmed using fluoroscopy.

- Device opening pressure is set according to intraventricular opening pressure (IVOP). The device is programmed 10 cm H2O below this value.

After surgery, patients stay for 48 hours as inpatient for close postoperative follow-up. During these 48 hours, physical rehabilitation specialist designs an individual rehabilitation plan. Again, education on device care, hygiene and urgent signs that may require visit to the emergency room are provided.

Patients are discharged on the third postoperative day. A control CT scan is ordered, and patients are instructed to visit their surgeon on the tenth postoperative day at the outpatient clinic.

10.1.5 Phase 5 (follow-up)

Patients are followed on months 1, 3, 6 and 12 after surgery. The main objective is to evaluate shunting device functionality and symptom improvement. Psychology tests are performed on months 6 and 12. Rehabilitation plans are adjusted according to every individual's needs.

11. Conclusions

Despite the huge amount of research since its original description, NPH remains an underdiagnosed disorder due to lack of clinical suspicion amongst the medical community. Therefore, the main concern is raising interest and suspicion amongst all medical professionals.

Recent advances in diagnostic imaging and lab biomarkers have given interesting insight into the pathophysiology of NPH that will probably be fundamental in the future. The best proven method for diagnosing and treating patients with NPH is following a standardized multidisciplinary protocol.

Conflict of interest

None of the authors have any conflict of interest to disclose.

Abbreviations

AChE	Acetyl cholinesterase
AC-PC	Anterior commissure-posterior commissure plane
AD	Alzheimer's dementia
APP	Amyloid precursor protein
AQP4	Aquaporin 4 channels
ASL-MR	Arterial spin-labeling magnetic resonance
ASV	Aqueduct stroke volume
BBB	Blood–brain barrier
BuChE	Butyryl cholinesterase
CA	Callosal angle
CAI	Carbonic anhydrase inhibitor
CAPPAH	Convexity apparent hyperperfusion
CBF	Cerebral blood flow
CSF	Cerebrospinal fluid
CSFBB	Blood-cerebrospinal fluid brain barrier
CNS	Central nervous system
COE	Center of excellence
CPP	Cerebral perfusion pressure
CT	Computed tomography

CVP	Central venous pressure
DESH	Disproportionately enlarged subarachnoid space hydrocephalus
DTI	Diffusion tensor imaging
DSIP	Delta sleep-inducing protein
EI	Evans' index
ETV	Endoscopic third ventriculostomy
FA	Fractional anisotropy
FDA	Food and Drug administration
FDG	Fluorodeoxyglucose
FIM	Functional independence measurement
FLAIR	Fluid attenuated inversion recovery
FSFB	Fundación Santa Fe de Bogotá
FTD	Frontotemporal dementia
GABA	Gamma-aminobutyric acid
GBP	Great British pound
GFAP	Glial fibrillar acid protein
5-HIIA	5-Hydroxyindoleacetic acid
HVA	Homovanillic acid
ICH	Intracranial hypertension
ICP	Intracranial pressure
ICP_{SA}	Subarachnoid space intracranial pressure
ICP_{SS}	Sagittal sinus intracranial pressure
ICIQ-SF	International consultation on incontinence questionnaire – short form
IFS	INECO frontal screening
IVOP	Intraventricular opening pressure
JCI	Joint Commission International
LP	Lumbar puncture
LPS	Lumbo-peritoneal shunt
MAP	Mean arterial pressure
MBP	Myelin basic protein
MHPG	3-methoxy-4-hydroxyphenylglycol
MIT	Massachussets Institute of Technology
MMSE	Mini-mental state examination
MRI	Magnetic resonance imaging
mRNA	messenger ribonucleic acid
NEJM	New England Journal of Medicine
NGF	Neural growth factor
NFL	Neurofilament light chain
NPH	Normal pressure hydrocephalus
NPY	Neuropeptide Y
NRGN	Neurogranin
NSE	Neuron specific enolase
PAI	Plasminogen I activator inhibitor
PC-MR	Phase contrast magnetic resonance
PET	Positron emission tomography
PGDS	Prostaglandin D synthase
PPV	Positive predictive value
QALY	Quality-adjusted life year
R_{CSF}	CSF outflow resistance
Re	CSF reabsorption
SINPHONI	Shunt for idiopathic normal pressure hydrocephalus open-label randomized trials

SAD	Subcortical arteriosclerotic dementia
SAS	Subarachnoid space
SOM	Somatostatin
SPECT	Single photon emission computed tomography
SPLIT	Time-spatial labeling inversion pulse
TNF	Tumor necrosis factor
USD	United States dollar
VAS	Ventriculo-atrial shunt
VEGF	Vascular endothelial growth factor
VIP	Vasoactive intestinal peptide
VPlS	Ventriculo-pleural shunt
VPS	Ventriculo-peritoneal shunt

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