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Review

# From the past to the present: evolving theories in the pathophysiology of normal pressure hydrocephalus

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## ABSTRACT

Over recent decades, various hypotheses and theoretical frameworks have been advanced to elucidate the aetiology of normal pressure hydrocephalus (NPH). This reversible neurological condition, characterised by the classical clinical triad of gait disturbance, urinary incontinence and cognitive impairment, represents a multifactorial interplay of pathophysiological processes that co-occur, rather than originating from a single, defined cause. Despite extensive research efforts, the precise aetiology and underlying pathophysiological pathways remain indeterminate. Contributory factors such as dysfunction of the glymphatic system, diminished arterial pulsatility, metabolic and osmotic dysregulation, astrogliosis and neuroinflammatory processes are acknowledged as critical in the pathogenesis of NPH. Recent advancements in the understanding of these pathophysiological aberrations have substantially refined the conceptualisation of the NPH phenotype, enhancing the predictive accuracy for cerebrospinal fluid diversion interventions. This review addresses the definition and classification of NPH and emphasises future research directions aimed at further elucidating the molecular and physiological mechanisms underlying the disease. A comprehensive understanding of this syndrome is critical for informed clinical decision-making and optimising therapeutic outcomes. With the global increase in ageing populations, accurately differentiating NPH from other neurodegenerative disorders and managing overlapping comorbidities has become increasingly significant.

## INTRODUCTION

Dementia is a significant concern in contemporary society, currently affecting approximately 50 million individuals globally, with this number expected to double by 2050.[1] Normal pressure hydrocephalus (NPH), often regarded as a differential diagnosis in cases of dementia, is anticipated to impact from 10 per 100 000 to 22 per 100 000 people (for probable idiopathic NPH (iNPH)) and 29 per 100 000 people (for possible iNPH) in the elderly population, increasing with higher age.[2–5] Nonetheless, extensive underdiagnosis globally reduces these figures, with actual prevalence likely being much greater. The socioeconomic and healthcare burdens are substantial, yet available treatments could help reduce the growing pressures on health systems.[6] The primary cause of underdiagnosis stems from the complexities involved in differentiating NPH from other neurodegenerative or cerebrovascular disorders. Factors such as age, risk factors and overlapping clinical symptoms or imaging signs can mimic syndromes such as Alzheimer's disease (AD), Parkinson's disease (PD), Lewy body disease, vascular dementia, progressive supranuclear palsy and other conditions.[7] Due to the high prevalence of these disorders among the elderly, numerous NPH patients might also have neurodegenerative comorbidities.[7]

However, unlike other disorders with cognitive decline, the progression of NPH can be partially reversed through shunt implantation.[8] Therefore, it is crucial for anyone involved in the care of dementia patients to be well-acquainted with this diagnosis as there is a growing necessity for more effective shunt candidate selection and improved efficiency in NPH treatment. Although there are potential risks, especially in terms of surgical complications,[9 10] the majority of surgical treatments for NPH result in not only clinical improvement but also an enhanced quality of life.[11 12] The significance of treatment is evident in its positive impact on the prognosis of NPH patients and the maintenance or improvement of their clinical profiles, as up to 70% of shunted patients improve after treatment in a long-term perspective.[13] Conversely, this raises the question of the potential benefits of shunt therapy for patients who do not have a pure NPH diagnosis but could still gain from permanent cerebrospinal fluid (CSF) drainage despite having an additional neurodegenerative disorder.

To facilitate proper shunt-candidate selection, it is imperative to first understand the underlying causes of NPH. This task is challenging due to the syndrome's complexity, its chronic and progressive nature and the overlap of comorbidities, which complicate not only differential diagnoses of dementia but also the physiological ageing processes that remain incompletely understood. This review aims to examine historical concepts of NPH pathophysiology and provide a comprehensive overview of the latest findings in both physiological and pathophysiological brain mechanisms. These insights are relevant to neurodegenerative research and may enhance decision-making regarding NPH patients.

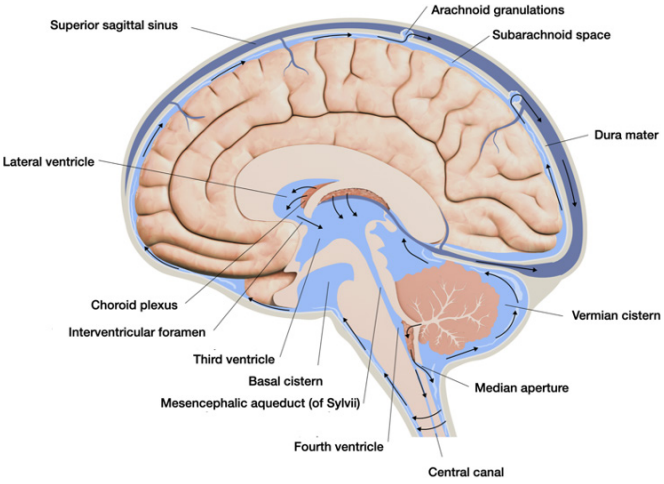


**Figure 1** Traditional understanding of CSF circulation. CSF, cerebrospinal fluid.

## CSF PHYSIOLOGY AND THEORY BEHIND HYDROCEPHALUS DEVELOPMENT

### Intracranial hydrodynamics: volumes and CSF circulation

A substantial proportion of CSF that enters the brain is actively synthesised by the choroid plexi located within each ventricle.[14] These choroid plexi, characterised by their permeable epithelial lining, are responsible for the production of CSF in the lateral, third and fourth ventricles. The volume of CSF generated by each ventricle exhibits interspecies variability; in humans, the choroid plexi in the lateral ventricles play a particularly critical role due to the comparatively larger surface area of the cerebral cortex relative to that of the posterior fossa. Conversely, in species such as cats, dogs, rabbits and even rhesus monkeys, the choroid plexus in the fourth ventricle may contribute a greater volume of CSF than that produced in the lateral ventricles.[15] This variability underscores the adaptive mechanisms of CSF production in response to the anatomical and physiological demands of different species.[16 17]

The standard circulation of CSF within the ventricular system is delineated in figure 1. Historically, CSF dynamics have been elucidated through two predominant theoretical frameworks: (1) the bulk flow model and (2) the pulsatile flow model.[18]

The bulk flow model postulates that hydrostatic forces generate a pressure gradient between the choroid plexuses, the anatomical structures responsible for the synthesis of CSF under elevated pressure conditions, and the arachnoid granulations, which facilitate the absorption of CSF at comparatively lower pressure levels.[18 19] According to this model, CSF traverses a unidirectional pathway, initiating from the lateral ventricles and progressing to the third ventricle via the foramen of Monro. Subsequently, CSF advances to the fourth ventricle through the Sylvian aqueduct. Ultimately, CSF exits the ventricular system either into the central canal of the spinal cord or the subarachnoid space through the lateral foramina of Luschka and the median foramen of Magendie.

The understanding of CSF circulation is essential for elucidating the pathophysiological mechanisms underlying various neurological conditions, including iNPH. Investigating these dynamics provides critical insights into the maintenance of intracranial homeostasis and the implications of altered CSF flow on cerebral function.

Recent phase-contrast MRI studies have fundamentally challenged the traditional bulk flow model of CSF circulation. These investigations reveal that CSF dynamics are not solely reliant on simple bulk flow; rather, they are influenced by multiple factors, including arterial pulsatile flow, jugular venous pressure and respiratory waves. Consequently, fluctuations in CSF pressure can be observed, typically ranging from 10 to 15 mm Hg in healthy adults and 4–5 mm Hg in infants.[20–22] New models advocate for a more integrated approach that incorporates both bulk and pulsatile flow, accommodating to-and-from movements and fluid exchange between the blood-brain border (BBB) and interstitial fluid (ISF).[23–25]

Phase-contrast MRI studies indicate that net CSF flow is superimposed on larger oscillatory movements driven by hydrostatic pressure changes caused by variations in blood volume within the brain.[15] These oscillations are synchronous with the cardiac and respiratory cycles. For example, during systole, the increased blood volume in the cranium pushes CSF into the vertebral subarachnoid spaces. This outward flow primarily originates from the cranial subarachnoid spaces, with some contribution from the ventricles. Conversely, during diastole, the flow reverses.

### Fluid interchange

Both solute and fluid exchange between CSF and ISF occurs across two critical interfaces: the ependymal lining of the ventricles and the pial layer, which separates the parenchyma from the subarachnoid spaces.[26] Convective movements of ISF significantly enhance the exchange between CSF and ISF through white matter into the ventricles, as well as facilitate the movement of ISF and/or CSF through perivascular spaces associated with blood vessels that course between the parenchyma and the subarachnoid spaces. CSF is secreted by the choroid plexuses (figures 2 and 3) into the brain ventricles, where it subsequently flows to sites of outflow into lymph or blood.[27–29] There is also a rapid exchange of water and various solutes across the brain microvessels forming the BBB, contributing further to CSF composition.

The endothelial cells lining the brain's vasculature, which create the BBB, provide a large surface area for the exchange of fluids and solutes between ISF and blood. The BBB plays a critical role in the rapid influx and efflux of substances like water, oxygen, carbon dioxide and glucose.[30] However, the exchange of sodium and chloride ions across this barrier is relatively limited compared with exchanges occurring over the longer distances between most ISF and CSF compartments. This discrepancy arises from the unique properties of the endothelial cells at the BBB, which are tightly joined by junctions that significantly restrict paracellular transport of ions such as sodium and chloride ions (figure 2).

### Glial involvement

The glial network is a complex and interconnected system of glial cells that supports neural activity and maintains brain homeostasis. Microscopically, this network is characterised by glial endfeet, which surround cerebral blood microvessels and form a key component of the BBB. These endfeet are highly permeable, more so than the endothelial layer itself, due to the presence of small gaps and specialised aquaporin-4 (AQP-4) water channels embedded in their membranes.[31 32] These channels enhance water permeability, playing a critical role in fluid regulation and nutrient exchange in the brain.

Glial cells communicate through several mechanisms, including direct intercellular connections such as gap junctions and tunnelling nanotubes. Gap junctions are formed by connexins

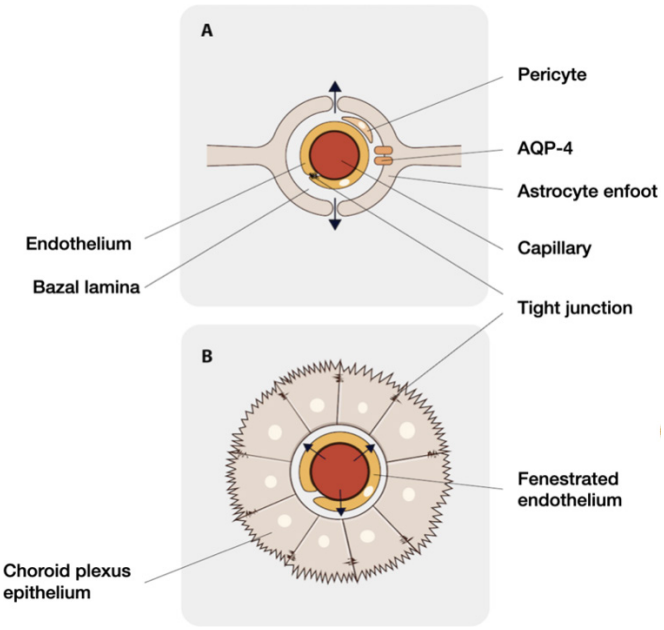


**Figure 2** CSF physiology at the cellular level. Images (A, B) depict characteristic cells included in BBB (A) and blood–CSF barrier (BCB) found in the choroid plexus. AQP-4, aquaporin-4; BBB, blood–brain border; CSF, cerebrospinal fluid.

(Cxs), a family of transmembrane proteins that assemble into hemichannels and subsequently into full gap junctions.[33] Key connexins, such as Cx29, Cx32, Cx36, Cx37, Cx43 and Cx47, are expressed in various brain cells, including oligodendrocytes, neurons, astrocytes and endothelial cells.[34] These junctions allow the exchange of ions, second messengers and small metabolites, thereby enabling intracellular signalling and metabolic coordination across the network. Most of this evidence regarding the distribution and roles of connexins stems from rodent and other experimental models.[33–36] Although expression patterns of Cxs are presumed to be conserved in humans, direct human evidence, particularly in the context of iNPH, remains limited and largely extrapolated from animal studies. Calcium ion waves and vesicle-mediated signalling further contribute to glial communication and modulation of neuronal activity. These phenomena have been well characterised in in vitro and animal models, showing that while connexins share core functions, different subtypes vary in conductance, permeability and cellular distribution.[35 36]

The integrity of this glial network can be disrupted by structural and molecular changes, with significant implications for

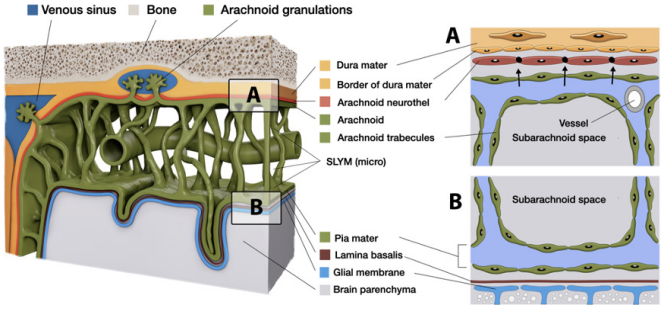


**Figure 3** Modern perspective on CSF physiology and the anatomy of meningeal layers. CSF, cerebrospinal fluid; SYLM, subarachnoid lymphatic membrane.

neurodegenerative diseases.[37] Specifically in iNPH, human neuropathological studies have identified vascular alterations in cortical capillaries, including thinning of the basement membrane between astrocytic endfeet, endothelial cells and pericytes, as well as compromised BBB integrity.[38] These changes impair both fluid homeostasis and neuronal function.

Importantly, reduced expression of AQP-4 in astrocytic endfeet and the surrounding neuropil has been demonstrated in human brain tissue from iNPH patients, with immunohistochemical analyses showing disrupted localisation of AQP-4 along perivascular regions.[38 39] AQP4 plays a central role in regulating water movement between the CSF, ISF and blood compartments, and its mislocalisation is associated with impaired glymphatic clearance and extracellular fluid accumulation.

Similarly, a reduction in the dystrophin isoform Dp71 has been observed in human iNPH samples.[38] Dp71, the predominant dystrophin isoform in the brain, is critical for anchoring AQP-4 and ion channels to the astrocytic endfeet via the dystrophin-associated protein complex (DAPC).[40] Loss of Dp71 disrupts the structural integrity of perivascular astrocytes and is associated with a shift from normal to pathological mitochondrial profiles, further undermining glial support of neuronal function. While the core roles of Dp71 and DAPC in anchoring membrane proteins have been well described in both human tissues and experimental models, the specific mitochondrial abnormalities in iNPH have so far been demonstrated primarily through human postmortem studies and biopsy-based analyses.[38]

Beyond iNPH, deregulation of the glial network is implicated in other neurodegenerative disorders, including AD and various forms of dementia.[41] This broader body of literature is supported by both experimental models and human neuropathological studies, where impaired glial communication, mislocalisation of AQP-4, altered connexin expression and loss of anchoring proteins contribute to disturbed fluid regulation, disrupted metabolic signalling and progressive neuronal dysfunction.

## Outflux from the brain

### Arachnoid Villi

The principal site of CSF absorption is the Pacchionian granulations, or villi, which facilitate drainage into the venous sinus.[42 43] This pathway typically begins to develop around the age of seven and continues to mature until approximately 20 years of age, as evidenced by radiological studies of arachnoid granulations.[43] Although arachnoid granulations may initiate function in late infancy, CSF dynamics during this developmental period must rely on alternative drainage pathways, as the maturation of arachnoid granulations during childhood is contingent on the aggregation of individual arachnoid villi into macroscopic clusters.[44] Arachnoid cell clusters observable in the fetal period serve as precursors to the arachnoid villi and granulations that form later in life.[45]

The alternative, or ‘minor’, CSF drainage pathways include:

1. **Perineural space:** Channels CSF to the lymphatic system.
2. **Perivascular and lymphatic route:** Directs CSF to the perivascular spaces and lymphatic system and effluxes from the skull.
3. **Transependymal-interstitial route:** Directs CSF to the perivascular and subpial spaces within both the brain and spinal cord.
4. **Choroid plexus epithelium:** Facilitates drainage into fenestrated capillaries.

In rodents, small mammals and the developing immature human brain—where arachnoid granulations are either absent or

not fully developed—these minor pathways serve as the primary conduits for CSF dynamics.

### Perineural routes

The importance of cranial perineural routes, particularly concerning the olfactory nerve traversing the cribriform plate, has been well-documented in various animal species, including cats, rats, mice, rabbits, sheep and non-human primates.[46] However, the significance of this route in humans remains ambiguous, as various reports have indicated tracer delivery through the cribriform plate into the nasal mucosa. Melin *et al*[47] proposed that the cribriform plate may represent a minor elimination route in humans. Alternatively, their data might support either (1) a closed-loop model connecting the perineural routes via the plate and lymphatics or (2) sufficiently rapid removal of contrast agent gadobutrol through lymphatic or venous outflow, which would maintain low concentrations in the nasal mucosa.[46 48 49]

Experimental studies demonstrate that intranasal drug administration can enable direct delivery to the brain, a phenomenon that would be challenging to explain if CSF outflow were nonexistent through this route.[48] Consequently, it can be concluded that while the significance of CSF outflow via the cribriform plate in humans is not trivial, its relative importance remains uncertain.

### Perivascular and lymphatic routes

Substantial evidence supports the efflux of substances to lymphatics within the cranial meninges or at the base of the skull (figure 3).[50 51] However, the precise proportion of fluid outflow through these pathways remains unclear. The absence of alterations in intracranial pressure (ICP) or brain fluid volumes following the ablation of meningeal lymphatics may indicate either that these lymphatics play a minor role in fluid outflow or that compensatory mechanisms occur within other outflow pathways and/or CSF production rates subsequent to their removal.[52] Direct outflow from the brain parenchyma to lymphatics may be particularly significant, as it provides a mechanism for ISF drainage that bypasses mixing with CSF in the ventricles or subarachnoid spaces.[53]

The relative significance of various outflow routes is contingent on different physiological conditions. Notably, a study by Stanton *et al*[54] revealed that under ketamine/xylazine anaesthesia in mice, the primary outflow occurred through the cribriform plate. Conversely, when isoflurane anaesthesia was administered, the principal outflow shifted to cranial nerves originating from the brainstem, with a lesser contribution from spinal routes. Thus, while the major sites of outflow may vary, neither prominently features outflow from the cortical subarachnoid space.

Given the potential implications of alterations in outflow routes for conditions such as hydrocephalus, further investigation is imperative to elucidate outflow pathways in humans.[55] Regardless of the specific pathways involved, the overall rate of outflow significantly increases as ICP rises.[15 56 57]

### Transependymal-interstitial route

The transependymal-interstitial route of CSF outflow involves the passage of CSF across the ependymal lining into the brain parenchyma and subsequently into the interstitial space. This process is supported by the concept of the ependyma as a physical border, which helps explain the concentration differences between extracellular fluid and CSF through transependymal flow. In this mechanism,[19 24 58] CSF transports infused compounds from the ventricles into the brain parenchyma, facilitating the equilibration of concentrations between CSF and brain extracellular fluid. The rapid turnover of CSF maintains a low concentration gradient within the ventricles. This pathway, while potentially serving as an auxiliary drainage route when traditional CSF outflow mechanisms are impaired (eg, in hydrocephalus or elevated ICP), is often linked to pathological conditions. Its activation may contribute to tissue oedema and disrupt neural function, underscoring its complex role in both physiological and pathological states.[59]

### Choroid plexus epitehlium

The choroid plexus plays a pivotal role in the interchange of fluids and solutes between the bloodstream and CSF, acting as both a site of CSF production and a mediator of molecular exchange.[14 24 60] Through active transport and selective permeability, the choroid plexus regulates the composition of CSF, maintaining homeostasis and facilitating the clearance of metabolic waste. This dynamic interchange ensures the supply of nutrients and signalling molecules to the central nervous system (CNS) while preserving the ionic balance crucial for neuronal activity. Additionally, the choroid plexus contributes to CSF outflow, interacting with arachnoid granulations, perivascular spaces and lymphatic-like drainage systems to sustain the turnover and circulation of CSF.[15] Under pathological conditions, such as inflammation or impaired CSF drainage, disruptions in this fluid interchange can exacerbate ICP, alter solute dynamics and impair neural function, highlighting its integral role in both normal and diseased states.

## Classical theory behind hydrocephalus

The definition of hydrocephalus remains contentious due to its broad nature, encompassing various clinical aspects and manifestations. Consequently, it is not likely that a singular definition can adequately encompass all its forms. The most encompassing interpretation considers hydrocephalus as the condition characterised by (1) abnormalities in CSF circulation, production or absorption, coupled with (2) ventriculomegaly.[61]

In infants, ventriculomegaly may occur without substantial loss of brain parenchyma, as the flexible, expanding skull can accommodate the enlarging ventricles without a corresponding reduction in cortical volume.[62 63] Nevertheless, as the infant matures, the brain's parenchymal volume may continue to increase; however, the cortex typically expands into a thinner layer. This morphological alteration can adversely impact long structures, such as axons and blood vessels, which are less pliable and unable to stretch significantly.

In contrast, in adults, where the skull is rigid, the total volume within the cranial cavity—including blood and vessel walls, CSF, ISF, intracellular fluid and solid components of the brain—must equate to the volume of the available cranial space.[61] This principle, articulated by Monro and Kellie, suggests that any increase in the volume of these constituents would elevate ICP.[64] Such an increase could potentially herniate the cerebellar tonsils through the foramen magnum, obstructing venous drainage and CSF pathways, which may lead to further increases in ICP and possibly fatal outcomes. Consequently, ventriculomegaly in adults must coincide with reductions in the volume of other cranial contents, which may include:

- A modest decrease in blood volume within the cerebral vasculature.
- Alterations in the parenchymal structure, such as cellular loss, cellular shrinkage due to dehydration or the depletion of cellular components, including myelin.

- A reduction in CSF volume within the subarachnoid spaces.
- A decrease in ISF within the parenchyma.[15]

These observations also bear relevance to the classification of hydrocephalus, given that the skull can expand in infants, while the rigid adult skull precludes this possibility, leading to well-characterised clinical manifestations.[61 62]

Hydrocephalus can be classified into non-communicating and communicating forms.[65] Non-communicating hydrocephalus occurs when CSF flow through or out of the ventricles is obstructed, with a classic example being obstruction of the cerebral aqueduct, often due to tumours or vascular malformations. Conversely, communicating hydrocephalus is a broader category that cannot be attributed to a single aetiology.[15]

Rather than strictly separating communicating from non-communicating forms, it is more practical to consider variations in the sites of obstruction and the extent of communication. At one extreme, certain conditions permit unrestricted communication through the ventricles and subarachnoid spaces but exhibit defects in CSF outflow, as seen in paediatric external hydrocephalus and adult idiopathic intracranial hypertension (IIH).[15] At the opposite extreme, conditions such as complete aqueductal stenosis demonstrate a lack of communication between the ventricles and subarachnoid spaces, although without defects in outflow routes.[15 61 63 66] Intermediate conditions reveal varying degrees of flow restriction within the brain, affecting access to certain compartments.

The term 'hydrocephalus' is rarely applied to instances of CSF accumulation associated with brain atrophy, as seen in AD or PD.[67–69] This phenomenon is referred to as 'hydrocephalus ex vacuo' to differentiate it from classical hydrocephalus. Notably, NPH represents a distinct form of hydrocephalus, exhibiting a pathophysiology that markedly diverges from other types of hydrocephalus.[70]

## HAKIM'S AND ADAM'S DISCOVERY OF NPH

Prior to the seminal contributions of Salomón Hakim and Raymond Adams in 1965,[71] the literature addressing symptoms of adult hydrocephalus was sparse, encompassing only three notable publications. Riddoch's study in 1936 primarily focused on tumours of the third ventricle, while McHugh documented cases of congenital occult hydrocephalus. Foltz and Ward [72] reported a case of communicating hydrocephalus resulting from subarachnoid haemorrhage. The groundbreaking work of Hakim and Adams established NPH as a distinct clinical entity characterised by a triad of symptoms: gait disturbances, cognitive decline and urinary incontinence.

Salomón Hakim, born to Lebanese immigrants and raised in Colombia, nurtured a profound interest in both physics and medicine, ultimately becoming a prominent neurosurgeon in the mid-20th century. In 1957, he made a significant observation at San Juan de Dios Hospital in Bogotá, identifying what he termed 'symptomatic occult hydrocephalus'. He successfully treated a teenage patient exhibiting ventriculomegaly yet displaying normal ICP by employing cerebrospinal fluid drainage, which resulted in substantial recovery. Hakim hypothesised that enlarged ventricles could exert excessive mechanical force despite the maintenance of normal pressure, a phenomenon he referred to as the 'hydraulic press effect'.

In 1958, he treated a trombone player presenting with gait, cognitive and urinary symptoms and observed marked improvement following CSF drainage and the implantation of a shunt. Despite facing initial scepticism from the medical community, the research conducted by Hakim and Adams laid the groundwork for subsequent investigations and significantly advanced the understanding of NPH. Their findings underscored the importance of recognising and addressing this condition, ultimately contributing to improved diagnostic and therapeutic strategies in the field of neurology.

## THE EVOLUTION OF PATHOPHYSIOLOGICAL UNDERSTANDING OF NPH SINCE HAKIM'S ERA

### General principles and vascular factors

Research into the pathophysiology of NPH has predominantly focused on the mechanical facets of the condition. Ventricular enlargement typically arises from an accumulation of CSF within the ventricular system, which is attributed to delayed CSF outflow through previously delineated pathways.[73] This accumulation exerts heightened mechanical stress on the periventricular white matter, resulting in axonal hypoxia and ischaemia.[74] In patients with NPH, this process is chronic, exacerbated by the natural brain atrophy that accompanies ageing.[75] Prolonged ventriculomegaly and alterations in the periventricular white matter contribute to damage to the ependymal lining of the ventricles, which gradually loses its plasticity. This results in decreased compliance and leads to the so-called 'stiff ventricle' state.[76 77] Consequently, prevalent radiological findings in NPH patients, such as transependymal transudation and periventricular oedema, reflect these phenomena, as initially described in the pulsatile and bulk flow theories of CSF circulation at the commencement of the 21st century.

As ICP rises and cerebral blood flow (CBF) and cerebral perfusion pressure fluctuate, disruptions at the molecular level begin to manifest.[78] These include metabolic and biochemical alterations that result in demyelination owing to oligodendroglial damage.[79 80] Mechanisms governing water homeostasis subsequently lead to an accumulation of ISF, which elevates interstitial transmantle pressure.[75 81] This pressure increase may precipitate thrombosis of cerebral deep veins, obstruct CSF circulation, exacerbate transependymal transudation and inflict further damage on periventricular neurons and glial cells, thereby disrupting neurotransmitter release and metabolism.[58 82] Oxidative stress frequently results in an augmented risk of small artery and arteriolar spasm and thrombosis, which further contributes to cortical ischaemia, diminishes remyelination potential, elevates protein levels in the CSF and enhances gliosis and stiffness, culminating in a loss of compliance.[81 83 84] Periventricular astrocytes, in their attempt to replace apoptotic cells, become increasingly reactive and produce tumour necrosis factor-alpha (TNF-α). This cytokine is known to induce dysfunction within the neocortex and hippocampus, correlating with cognitive decline observed in patients with NPH.[85] Additionally, CBF is impaired in individuals with iNPH, leading to pathological perfusion characteristics.[86]

Furthermore, as delineated in the transmantle pressure gradient theory proposed in 1974,[87] pressure gradient between intraventricular ICP and cortical subarachnoid spaces becomes positive. This exacerbation of ventricular dilation creates a vicious cycle within NPH pathophysiology (figure 4).[81] Although CSF production remains constant, its accumulation within the ventricles escalates, outflow is delayed and pressure on the surrounding parenchyma intensifies due to persistent ventricular enlargement. The metabolic alterations in the periventricular white matter further expand and augment the cortical subarachnoid space, prolonging the disruption of CSF outflow and its accumulation in the ventricular system.[7 75 80 88 89]

Within the context of iNPH, arterial hypertension and diabetes mellitus are well-documented vascular risk factors.[90]

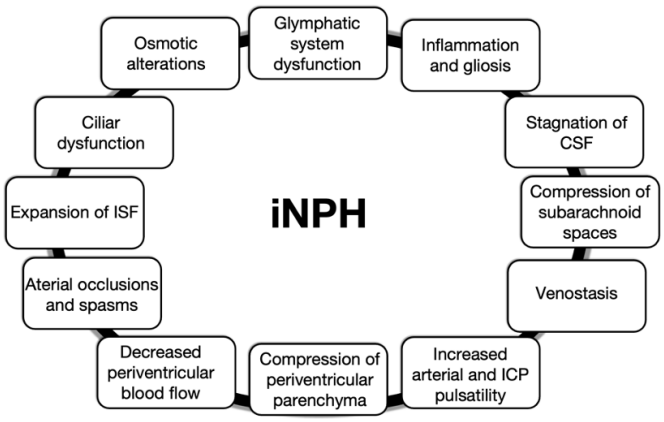


**Figure 4** A diagram of multifactorial understanding of iNPH pathophysiology. CSF, cerebrospinal fluid; ICP, intracranial pressure; iNPH, idiopathic normal pressure hydrocephalus; ISF, interstitial fluid.

Prior investigations have delineated reduced CBF and low-grade ischaemia, indicating compromised cerebrovascular function associated with this pathology, which is commonly observed in the ageing brain.[91] Due to physiological alterations inherent to ageing, arterial compliance diminishes, culminating in a reduction of arterial pulsatility.[92] This decrease in arterial pulsatility subsequently precipitates an elevation in pulsatile flow within the Sylvian aqueduct, serving as a compensatory mechanism for diminished arterial pulsatility. These findings suggest that modifications in vascular elasticity, along with consequent alterations in pulse wave transmission, are linked to fluctuations in arterial pressure throughout the cardiac cycle.[92 93]

The modifications in ICP pulse waves were rigorously examined by Eide and Stanisic in 2010.[94] Their study, which encompassed 40 patients diagnosed with definite iNPH, identified the amplitude of ICP pulse waves as a critical determinant of patient responsiveness to shunt treatment. Their research elucidated the correlation among ICP, CSF pressure and the compliance of intracerebral parenchyma, emphasising that alterations in these parameters reflect neurophysiological changes and are associated with the emergence of cognitive deficits.

A recent study further investigated ICP pulse waves in both iNPH and late-onset idiopathic aqueductal stenosis (LIAS).[21] The study found that ICP values were higher in LIAS compared with iNPH, while the amplitude of the heartbeat-related pulse wave—measured in both the frequency and time domains—was greater in iNPH patients. These findings support the hypothesis that elevated ICP pulse wave amplitudes contribute to the pathophysiology of iNPH.

## CSF hydrodynamic mechanisms

However, more nuanced insights reveal that CS dynamics are governed by a complex interplay between pulsatile intracranial compliance, perivascular (glymphatic) exchange, and ventricular wall biomechanics. A hallmark feature of altered CSF dynamics in iNPH is the presence of increased aqueductal CSF stroke volume (SV), measured as the volume of CSF that oscillates back and forth through the cerebral aqueduct during each cardiac cycle. In healthy adults, the normal aqueductal CSF SV ranges from 10 to 18 µL per cardiac cycle.[83] In contrast, patients with NPH often exhibit values exceeding 42 L per cycle, with some reports citing measurements as high as 60 L, as demonstrated in phase-contrast MRI studies.[95 96] This hyperdynamic flow is paradoxical because it occurs in the context of normal or only mildly elevated ICP. Clinically, aqueductal SV has gained prominence as both a diagnostic and prognostic biomarker. Multiple studies have demonstrated that preoperative aqueductal SV >42 uL is associated with favourable response to CSF diversion therapies.[95 96] Following shunt placement, normalisation of SV correlates with both symptom improvement and radiological reversal of periventricular hyperintensities.[97] Thus, elevated CS SV in NPH not only reflects underlying pathophysiology but also holds utility in guiding clinical management and evaluating therapeutic response. Importantly, shunting often results in a postoperative reduction of aqueductal SV towards normal ranges, supporting the hypothesis that ventriculomegaly in NPH is dynamic and partially reversible.

As proposed above, the pathophysiological mechanism underlying this phenomenon likely involves a loss of intracranial compliance. In a compliant system, arterial pulsations are dampened by the brain parenchyma, CSF and venous outflow structures. However, in NPH, ventricular wall stiffening, periventricular ischaemia and venous outflow impedance reduce this buffering capacity.[98] As a result, arterial pulsatility is transmitted more forcefully into the CS spaces, particularly the aqueduct, producing exaggerated bidirectional CSF motion during each systolic-diastolic cycle. The elevated SV is therefore not a reflection of increased CSF production or net flow but an indicator of disrupted pulsatile compliance within the intracranial compartment.

Additionally, studies have shown a temporal dissociation between arterial pulsations and CSF peak velocity, suggesting discoordination in the perivascular-CSF coupling system. Notably, Eide and Ringstad[28] demonstrated impaired glymphatic influx and perivenous clearance using intrathecal MRI contrast in NPH patients, implicating not only impaired bulk CSF turnover but also reduced neurofluid exchange at the capillary and interstitial levels. This has led to the proposition of a 'CSF stagnation hypothesis', whereby failure of both bulk and glymphatic circulation promotes toxin accumulation, neuroinflammation and ultimately, white matter tract disruption.

## The role of motile cilia

Recent investigations have identified motile ependymal cilia as crucial regulators of ventricular CSF flow and neuroepithelial integrity. Motile ependymal cilia have emerged as key regulators of CSF flow and homeostasis, with growing evidence implicating their dysfunction in the pathogenesis of iNPH. Both motile and primary (sensory) cilia have emerged as important regulators of CS dynamics and homeostasis, with dysfunction in either population increasingly implicated in the pathogenesis of iNPH.[99] Motile cilia are multiple, hair-like 9+2 microtubule structures present on the apical surface of ependymal cells lining the ventricular walls. They beat in coordinated metachronal waves, producing wall-near laminar flow that facilitates CS circulation, disperses solutes and supports glymphatic clearance.[100 101] These mechanistic insights have been primarily characterised through in vivo imaging and genetic models in experimental animals, including murine and zebrafish systems. This localised flow plays a crucial role in maintaining ventricular homeostasis by guiding CS along periventricular surfaces, reducing stagnation and preventing mechanical stress on the ependyma. In iNPH, histological analyses have revealed disrupted ciliary orientation, patchy ciliary loss and ependymal denudation, particularly in areas of ventricular distension and transependymal fluid flow,[102 103] findings derived from human postmortem neuropathological studies. This suggests that motile ciliary failure

contributes directly to the mechanical and biochemical alterations observed in periventricular tissue.

In contrast, primary cilia-non-motile 9+0 structures found singly on various CNS cell types function as mechanosensory and chemosensory organelles, transducing mechanical cues from CSF flow and regulating signalling pathways such as Hedgehog, Wnt and PDGF. In the choroid plexus epithelium, primary cilia are thought to participate in CS composition sensing, fluid balance regulation and potentially modulate secretion and transport of ions and metabolites, key processes that can affect intracranial volume and compliance.[104] These functional roles have been predominantly elucidated in animal models and in vitro studies, with limited direct evidence in human tissue. Disruption of primary cilia may therefore impair volume sensing or solute regulation, contributing to altered CSF osmolality and impaired reabsorption or production regulation—both processes implicated in the CSF imbalance seen in iNPH.

For instance, mice with targeted deletions of Foxi1, a transcription factor essential for ciliogenesis, develop communicating hydrocephalus with preserved ICP, mimicking features of NPH.[105] Similarly, mutations in dynein motor components such as DNAH5, Hydin and Pcp result in reduced ciliary motility and hydrocephalus with periventricular gliosis and white matter rarefaction.[106] These genetic and phenotypic findings come from murine and zebrafish models, though human genetic studies also support the role of dynein mutations in ciliopathies associated with hydrocephalus. Moreover, ciliary loss impairs local CSF mixing and glymphatic function, potentially exacerbating protein accumulation and interstitial oedema,[107] which are hallmarks of the disease's periventricular pathology, a phenomenon demonstrated primarily in rodent models using contrast-enhanced MRI. These findings suggest that motile cilia dysfunction is not merely epiphenomenal but may be an initiating factor in the altered hydrodynamics, ventricular dilation and white matter injury characteristic of iNPH.

## Molecular factors and loss of blood–brain barrier integrity

In instances of definite iNPH, a notable thinning of the basement membrane is correlated with the extravasation of the blood glycoprotein fibrinogen. Fibrinogen serves as an important biomarker for BBB integrity and is typically absent from the normal adult human brain parenchyma; however, trace amounts may be detected in the ageing population.[108] On exiting the vascular system, fibrinogen undergoes conversion to fibrin, a pro-inflammatory molecule that plays a substantial role in mediating inflammatory processes.[109] The role of fibrin(ogen) in neuroinflammation has been characterised in both human pathological studies and animal models of neurovascular injury.

Furthermore, there exists compelling evidence of reduced postsynaptic density length and a diminished number of functional mitochondria within presynaptic terminals.[110] However, reduction in postsynaptic density and a decreased number of mitochondria are more likely consequences of pathophysiological processes associated with NPH, which adversely affect neurons, rather than integral components of the primary pathophysiological mechanism of NPH. These observations imply impaired neuronal functionality, a significant concern given that cognitive impairment is a primary diagnostic criterion for iNPH.[111] It has been established in both ultrastructural human brain studies and corroborative experimental data in animal models that mitochondrial trafficking and distribution are intricately linked to synaptic activity, and an adequate supply of operational mitochondria is crucial for sustaining normal synaptic function due to the elevated energy demands of both presynaptic and postsynaptic terminals.[110 111] The observed reduction in postsynaptic density length in iNPH is particularly noteworthy, as this parameter serves as a proxy for synaptic strength and activity.[112] Additionally, the presence of oligomeric Aβ in proximity to the postsynaptic region has been shown to diminish postsynaptic density length, impair synaptic plasticity and augment synaptic loss in human neuropathological samples.[113 114]

In addition to vascular factors, alterations in ICP and CSF dynamics, as well as metabolic changes across various levels, inflammatory processes significantly influence the pathophysiology of iNPH, akin to the phenomena observed in neurodegenerative disorders.[85 115] Numerous studies have confirmed elevated concentrations of pro-inflammatory and anti-inflammatory biomarkers in patients diagnosed with iNPH[116]; these findings come from clinical CSF analyses employing immunoassays in human cohorts. However, distinguishing between iNPH and other neurodegenerative comorbidities remains challenging, particularly in light of findings that are frequently observed in ageing populations, including those with dementia. Specifically, cytokines such as interleukin 1 (IL-1), TNF-α, IL-β1, IL-6, IL-10 and transforming growth factor-beta 1 (TGF-β1) are among the most extensively discussed inflammatory biomarkers in the existing literature.[79 115] While their CSF concentrations may be elevated, the results remain heterogeneous, and the precise role of these biomarkers in the pathogenesis of iNPH has yet to be fully elucidated. Animal models have been employed to explore cytokine-mediated mechanisms; however, such models do not fully recapitulate the complexity of human iNPH.

## Glymphatic system, insights into brain lymphatics and their role in NPH

Historically, the absence of a lymphatic system facilitating the removal of excess fluid in the CNS has been described. The concept of meningeal lymphatics, described in 1787 by Paolo Mascagni[116] for the first time, has recently been enriched with new findings regarding the presence of both meningeal lymphatic vessels and the so-called glymphatic system described in 2012 using photon microscopy in rodents.[29] The glymphatic system refers to a system of perivascular spaces that facilitates the clearance of interstitial solutes and metabolic waste from the brain by using CSF flow across astrocytic endfeet AQP-4 channels (figure 5). It is particularly active during sleep,[117]

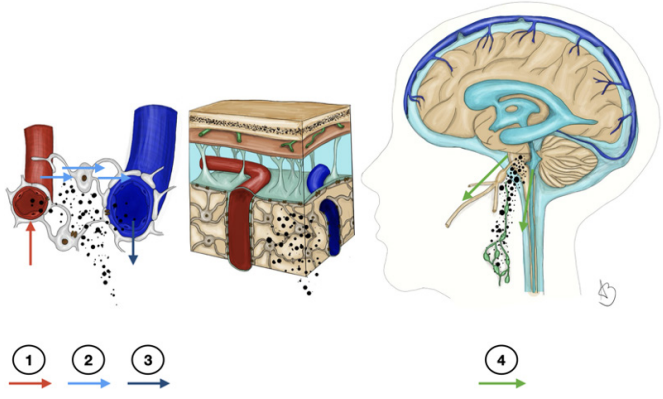


**Figure 5** Overview of glymphatic pathway processes. (1) Periarterial influx. (2) CSF-ISF interchange. (3) Perivenous efflux. (4) Perineural, perivascular and lymphatic outflux. CSF, cerebrospinal fluid; ISF, interstitial fluid.

aiding in removing neurotoxic substances such as Aβ and tau proteins, thereby contributing to overall neural homeostasis and health.[29 118] Additionally, it serves as a distributional network for much-needed energy substrates such as lipids, glucose and medications.[119] Since its discovery, plenty of studies have discussed the role of the glymphatic pathway and brain lymphatics, including the description of the fourth meningeal layer: subarachnoid lymphatic membrane.[51 120] Their role has been described particularly with regard to the expected impact on the pathogenesis of various diseases, including neurodegenerative diseases, traumatic brain injury, hydrocephalus or multiple sclerosis.[120 121]

Investigating the fluid dynamics between the ventricles, subarachnoid space and perivascular spaces is crucial for understanding the pathophysiology of iNPH. Aberrant CSF circulation in patients with iNPH is relatively well known; however, the exact pathogenesis remains elusive. According to Bateman,[88 122] patients with iNPH have significantly reduced venous drainage (due to stenosis of cerebral veins and sinuses) compared with healthy age-matched controls, which leads to a rising pressure in the cerebral vessels. This venous hypertension can, in turn, reduce the CSF absorption via the Pacchionian granulations, which causes the alternative route to adapt and potentially increases drainage via the glymphatic system. After a short ICP peak, the new equilibrium is reached with the glymphatic system compensating for the venous incompetence. Another way to explain the new equilibrium could be through reduced CSF production.[123] This 'latent stage' of the disease can persist until the patient's elderly years, when they develop deep white matter ischaemia (DWMI).[124 125] In physiological conditions, the CSF glides over the myelin due to high contents of fatty substances. Ischaemia leads to changes in the myelin properties, reduction of fat and relative increase of protein, causing the CSF's polar water molecules to be attracted to it, increasing the CSF outflow resistance.[126] DWMI then essentially acts as a dam, putting resistance to the CSF efflux through the glymphatic system, leading to fluid buildup and hydrocephalus.[127]

Schley *et al*[128] demonstrated that the propulsion of CSF into the brain interstitium is influenced by a pulse wave travelling along the arteries. Multiple studies have indicated that diminished cardiac activity and the subsequent reduction in pulse wave amplitude can decrease glymphatic flow, resulting in impaired cerebral perfusion.[57] Besides cardiac activity, the pulse wave is regulated by respiration-associated pressure changes in the thorax.[128] Recent studies using phase contrast-magnetic resonance imaging have shown that changes in CSF flow associated with respiration are greater in magnitude than those associated with the cardiac cycle. Another force driving the CSF into the interstitium is the pulsations of the ventricles which push CSF from its origin in the ventricular plexus to its point of reabsorption.[129] Although ventricular pulsations drive CSF macroscopically, they are ultimately a result of the arterial pulse wave.

It has been postulated that iNPH could be a '2-hit' hydrodynamic disease, the first phase represented by the deterioration of ventricular pulsations. The 'second hit' is characterised by reduced arterial pulsatility as a result of increased compression of the penetrating arteries caused by reduced efflux of the CSF.[130] Glymphatic clearance deterioration following the impaired CSF circulation would then lead to the accumulation of metabolic waste and neurotoxins, ultimately resulting in cognitive decline.[124] Bonney *et al*[124] speculated that iNPH is fundamentally a vascular disorder, especially because of high incidence of vascular risk factors in iNPH patients and finding of deep white matter and periventricular lesions. Those findings are considered to be the hallmarks of small vessel disease; they could, however, represent the second phase of Bradley's theorem.[131]

On the other hand, Bateman's work[88] attributes it to increased pressure on the venous end. Given that ventricular pulsations result from arterial pulsations, this initial phase could be termed the macrovascular phase. During this phase, the condition might be reversible. In later stages, patients develop DWMI, which according to Bateman[88] leads to fluid build-up. This aligns with Bradley's second hit hypothesis,[131] where increased fluid buildup compresses penetrating arteries and disrupts glymphatic function, potentially stemming from myelin changes in DWMI. This second phase could be referred to as the microvascular phase, supported by findings of small vessel disease markers in late-stage iNPH patients. Unlike the macrovascular phase, the microvascular phase is likely irreversible and is characterised by deterioration of the patient's symptoms.

Another hypothesis regarding the relationship between the glymphatic system and iNPH involves arterial compliance.[88] Reduced arterial compliance (as a result of atherosclerosis, eg) could disrupt the pulse wave dynamics, thereby affecting CSF circulation. This can partially explain the reversed flow of CSF. However, the causal relationship between these factors remains unclear. It is uncertain whether arterial stiffness is a cause or a result of impaired glymphatic function in iNPH.[124 132]

Additionally, as we described previously, decreased expression of AQP-4 has been proposed as a contributing factor to the pathogenesis of iNPH.[15 99] Reduced AQP-4 expression along perivascular spaces has been documented by Hasan-Olive *et al*[112] in iNPH patients, suggesting that impaired AQP-4 function may hinder the clearance of metabolic waste and CSF. This can in turn cause a buildup of metabolic byproducts leading to cognitive dysfunction.[31] It remains unclear whether reduced expression of AQP-4 is a cause or a consequence of iNPH pathophysiology.

The process by which metabolites and toxins are eliminated from the brain remains inconclusive, considering various studies reporting incompatible outcomes. The activity glymphatic system has been shown to be enhanced during sleep and anaesthesia, while being suppressed by wakefulness.[133] However, there is ongoing debate about both the structural routes and the mechanisms responsible for clearance. The glymphatic theory suggests that the movement of fluid, beyond simple diffusion, plays an active role in removing solutes from brain tissue during non-rapid-eye-movement (NREM) sleep.[118] It is thought that this flow is driven by hydrostatic pressure differences generated by arterial pulsations. Sedative doses of anaesthetics, which create conditions similar to deep NREM sleep, have also been found to enhance this clearance. Nevertheless, it is still unclear whether sleep indeed promotes greater clearance through increased fluid movement, as research presents evidence both in support and opposition to this hypothesis. A recent study performed by Miao *et al*[134] showed a reduction of CSF outflow in anaesthetised mice, and a completely opposite result followed in a study by Kroesbergen *et al*.[133] who used fluorescent fibre photometry to report that less tracer entered the brains of awake animals. Despite these unresolved results, good-quality sleep is generally recognised as significantly impacting long-term brain health. Studies have shown that superior sleep quality in adults is associated with a lower risk of developing mild cognitive impairment and AD. In contrast, sleep disturbances often precede a dementia diagnosis by several years. In murine studies, it has been demonstrated that various neuropeptides involved in the sleep-wake cycle (such as orexin or glucagon-like peptide 1) and their respective levels correlate with glymphatic drainage. Although the causality between the two factors has yet to be

proven, it could support the known connection between sleep quality and neurodegenerative disorders.[135–137] At this point, it is unclear how much of the decline in sleep quality is due to ageing itself or if it is primarily a result of the increased likelihood of health conditions that come with ageing. However, it is evident that good quality and sufficient sleep during adulthood is crucial for maintaining cognitive health in the elderly. Therefore, these results could hypothetically extend to iNPH; however, empirical data to substantiate this hypothesis is currently lacking, and it remains an area of research.

Furthermore, Román *et al*[138] identified a correlation between sleep-disordered breathing (SDB) and iNPH, highlighting the interaction between SDB and the glymphatic system during deep sleep phases, including REM and delta sleep. Regarding the reduction of muscle tone during a REM stage of sleep, relaxation of jaw and tongue muscles along with gravity causes the tongue and soft tissues to fall back into the throat, which leads to blockage of conductive airways, causing an obstructive sleep apnoea, one of the most common reasons for developing SDB. Among all of the apnoea-induced pathophysiological mechanisms which are linked to the iNPH that Román *et al* describe, one of them is a potential disturbance or fragmentation of a sleep cycle causing a patient to wake up during sleep, therefore causing an absence of REM sleep. A finding about a linkage between the importance of sleep and glymphatic system activity that is increased by 60% if present,[135] and in this case most likely not due to SDB, may give us another insight on how the glymphatic system contributes to the development and progression of iNPH in patients. This highlights the vicious-cycle-like nature of iNPH pathophysiology, where patients experience reduced deep and REM sleep, along with various degrees of circadian rhythm disruption. These factors are all associated with worsening cognitive performance and overall brain health, including impaired glymphatic system clearance.

Historical concepts discussing the novelties of CSF physiology, including summary of pathophysiological hypotheses surrounding hydrocephalus and/or NPH, are described in table 1.

**Table 1** Historical concepts discussing the novelties of CSF physiology along with related discussion over the pathophysiology of hydrocephalus and/or NPH

| Year of publication | Authors | Title |
|---|---|---|
| 1965 | Hakim and Adams[71] | Hakim-Adams Theory |
| 1974 | Hoff and Barber[87] | Barber Transcerebral mantle pressure gradient |
| 1993 | Greitz[42] | Restricted arterial pulsation hydrocephalus |
| 1994 | Raimondi[191] | A unifying theory for definition and classification of hydrocephalus |
| 2004, | Bateman[192] | Hemodynamic theory of venous congestion |
| 2006 | Oi and Di Rocco[193] | Evolution theory in cerebrospinal fluid dynamics and minor pathway hydrocephalus |
| 2008 | Rekate[194] | Importance of cortical subarachnoid space in understanding hydrocephalus |
| 2012 | Iliff *et al*[29] | A Paravascular Pathway Facilitates CSF Flow Through the A Paravascular Pathway Facilitates CSF Flow Through the Brain Parenchyma and the Clearance of Interstitial Solutes, Including Amyloid β |
| 2013 | Preuss[56] | Pulsatile vector theory |
| 2013 | Chikly and Quaghebeur[60] | Reassessing CSF hydrodynamics and novel hypothesis |
| 2013 | Xie *et al*[135] | Sleep Drives Metabolite Clearance from the Adult Brain |
| 2014 | Krishnamurthy and Li[195] | Osmotic gradient theory |
| 2016 | Matsumae *et al*[82] | Intimate exchange between cerebrospinal fluid and interstitial fluid |
| 2017 | Ammar *et al*[81] | The Comprehensive Idiopathic Normal-Pressure Hydrocephalus Theory (CiNPHT) |
| 2018 | Eide and Hansson[38] | Astrogliosis and impaired aquaporin-4 and dystrophin systems in idiopathic normal pressure hydrocephalus |
| 2018 | Ringstad *et al*[146] | Brain-wide glymphatic enhancement and clearance in humans assessed with MRI |
| 2019 | Román *et al*[138] | Sleep-Disordered Breathing and Idiopathic Normal-Pressure Hydrocephalus: Recent Pathophysiological Advances |
| 2019 | Eide and Ringstad[28] | Delayed clearance of cerebrospinal fluid tracer from entorhinal cortex in idiopathic normal pressure hydrocephalus: A glymphatic magnetic resonance imaging study |
| 2019 | Ahn *et al*[50] | Meningeal lymphatic vessels at the skull base drain cerebrospinal fluid |
| 2020 | Eide and Hansson[89] | Blood-brain barrier leakage of blood proteins in idiopathic normal pressure hydrocephalus |

Continued

## Genetic factors

Historically viewed as sporadic, a growing body of cohort studies and pedigree analyses may cluster within families, indicating a potential genetic component. The first documented case of familial iNPH appeared in a 1984 report, describing shunt-responsive iNPH in siblings.[139] Although candidate genes have been identified that show a correlation with the genetic origins of iNPH, most studies have been constrained by small sample sizes and incomplete analyses. Notably, up to 20% of iNPH patients have a relative who may also be affected, underscoring the growing importance of epidemiological research suggesting a hereditary contribution to iNPH pathophysiology.[140 141]

Several genes, such as *APOE3*, *AβPP*, *SFMBT1*, *CFAP43* and *CWH43*, have been linked to iNPH in various genetic investigations (see table 2). For example, a loss-of-function mutation in *CFAP43* was identified in a Japanese family with iNPH,[142] and inactivation of this gene in mice resulted in a hydrocephalus phenotype with ciliary abnormalities. Additionally, Yang *et al* found two loss-of-function deletions in *CWH43* through whole-exome sequencing of 53 iNPH patients, which may be implicated in iNPH.[143] A genome-wide association study (GWAS) conducted in the FinnGen Cohort[144] has provided important new insights into the genetic basis of NPH. This large-scale analysis included 1522 individuals with a clinical diagnosis of NPH

**Table 1** Continued

| Year of publication | Authors | Title |
|---|---|---|
| 2020 | Taghdiri *et al*[196] | Association between cerebrospinal fluid biomarkers and age-related brain changes in patients with normal pressure hydrocephalus |
| 2020 | Vallet *et al*[197] | Biomechanical response of the CNS is associated with frailty in NPH-suspected patients |
| 2021 | Bae *et al*[27] | Altered glymphatic system in idiopathic normal pressure hydrocephalus |
| 2021 | Kaczmarska *et al*[198] | Analysis of Intracranial Pressure Pulse-Pressure Relationship: Experimental Validation |
| 2023 | Møllgård *et al*[121] | A mesothelium divides the subarachnoid space into functional compartments |
| 2023 | Maeda *et al*[199] | Biomechanical effects of hyper-dynamic cerebrospinal fluid flow through the cerebral aqueduct in idiopathic normal pressure hydrocephalus patients |
| 2023 | Georgiopoulos *et al*[200] | Noninvasive assessment of glymphatic dysfunction in idiopathic normal pressure hydrocephalus with diffusion tensor imaging |

CNS, central nervous system; CSF, cerebrospinal fluid; NPH, normal pressure hydrocephalus.

and over 450 000 population-based controls, with genetic data linked to national health registry records. The study identified six genomic loci—*SLCO1A2*, *AMZ1*/*GNA12*, *MLLT10*, *CDCA2*, *PLEKHG1* and *C16orf95*—that showed a strong and statistically significant association with NPH ($p < 5\times10^{-8}$). These findings were further validated through meta-analysis with a replication cohort from the UK Biobank (n=173), demonstrating consistent effect sizes.

To assess genetic risk specific to iNPH, a subgroup analysis was performed excluding individuals with known secondary causes of hydrocephalus. In this iNPH-specific cohort (n = 1055), four of the six loci—*SLCO1A2*, *AMZ1*/*GNA12*, *MLLT10* and *C16orf95*—remained genome-wide significant. This strengthens the evidence that these variants are directly involved in the pathophysiology of idiopathic forms of the disease.

Functionally, the associated genes point to biological processes that are highly relevant to NPH, including the regulation of the BBB and CSF barrier, cerebrovascular function and ventricular fluid dynamics.[145] For example, *SLCO1A2* encodes an organic anion transporter that may influence CSF composition and clearance, while C16orf95 has been linked to brain ventricular volume regulation. These associations suggest a genetic contribution to impaired CSF homeostasis and structural brain changes observed in NPH. The most significantly associated genes, along with their putative roles in disease mechanisms, are described in more detail below.

***SLCO1A2:*** *SLCO1A2* encodes the organic anion transporting polypeptide 1A2 (*OATP1A2*), a sodium-independent transporter that facilitates the cellular uptake of various organic anions.[146] This transporter is primarily located apically in the endothelial cells of the brain's microvasculature, where it is integral to the transcellular pathway of the BBB and mediates the uptake of a diverse array of substrates. The importance of *SLCO1A2* in microvascular dynamics and BBB integrity is particularly pronounced when considering the vascular comorbidities frequently encountered in iNPH patients.[147] Notably, approximately 20% of CSF secretion is attributable to fluid transport across the BBB.[19 148 149] Disruptions in BBB function, such as protein leakage and fibrinogen extravasation, have been documented in iNPH. The deposition of fibrin within the brain parenchyma is associated with astrogliosis, and both fibrin extravasation and astrogliosis correlate with decreased expression of AQP-4.[89 108 109] This reduction is linked to glymphatic system dysfunction, further complicating the pathophysiological landscape in patients with iNPH.[27]

It is crucial to acknowledge that the expression of *SLCO1A2* has been associated with brain ageing.[150] This relationship implies that genetic variants within *SLCO1A2* are unlikely to be direct causes of congenital hydrocephalus. Instead, the upregulation of this gene may represent an adaptive response to ageing.[150] Certain genetic variants could impair the functionality of *SLCO1A2*, potentially rendering older individuals more susceptible to the development of NPH. This increased susceptibility may stem from compromised transport and clearance mechanisms across the BBB, the BCSF barrier and other interconnected pathways.[75 88 89 124 150]

***AMZ1* and *GNA12:*** Other genes, such as *AMZ1* and *GNA12*, play significant roles in various cellular processes. *AMZ1* encodes a metalloprotease that is integral to the degradation of extracellular matrix proteins,[151] while *GNA12* functions as a signalling protein involved in pathways regulating cell growth, differentiation and survival.[152] Their expression has also been associated with brain ageing,[153] akin to *SLCO1A2*. Dysregulation of either *AMZ1* or *GNA12* may contribute to neurodegenerative processes, manifesting as abnormal protein accumulation, cellular stress or apoptosis.[153] Notably, interference with the sphingosine 1-phosphate pathway, in which *GNA12* is implicated, has resulted in significant vascular alterations, causing an enlargement of the lateral brain ventricles by nearly fourfold.[154 155] Additionally, G protein-coupled receptor signalling, which includes G proteins like *GNA12*, has been correlated with the pathogenesis of hydrocephalus.[156]

Genes involved in amyloid metabolism: Altered amyloid metabolism is posited as a pivotal factor in the pathogenesis of iNPH.[157 158] Research indicates that individuals with iNPH demonstrate diminished concentrations of Aβ in CSF alongside reduced levels of soluble precursor proteins. The observed co-occurrence of AD and iNPH,[159] corroborated by findings from brain biopsies, has prompted the hypothesis that both conditions may share analogous underlying mechanisms. Aβ accumulation is widely recognised as a principal contributor to AD,[160] and proteins encoded by the apolipoprotein E (*APOE*) gene family play crucial roles in regulating Aβ.[161] Specifically, the *APOE4* allele is strongly associated with promoting amyloid deposition in the brain, a defining characteristic of AD.[162] However, investigations into potential correlations between the *APOE4* or *APOE3* genotypes and the iNPH phenotype have yielded inconclusive results.[163]

A study examining AD-related genetic loci and their influence on Aβ accumulation in iNPH found no significant associations. Pyykkö *et al*[164] further substantiated the absence of a link between *APOE4* and iNPH in a cohort of 202 iNPH patients and 687 controls, concluding that the *APOE4* allele does not constitute a risk factor for iNPH development. While the *APOE3* allele may be connected to iNPH in ways yet to be elucidated, the role of *APOE4* in this context appears minimal or negligible.

**Table 2** Candidate genes associated with iNPH pathophysiology

| Gene name | Gene product | Mutation/ variant/ expression change in iNPH | Function | Localisation in the CNS | Loci |
|---|---|---|---|---|---|
| *A1R and A2AR*[179] | Adenosine 1 receptor and adenosine 2A receptor | Decreased expression | Adenosine signalling | A1R—cortex, hippocampus, cerebellum, A2AR—striatum, olfactory bulb. | A1R—Ch 1q32.1 A2AR—Ch 22 q11.23 |
| *ADAM10*[165] | Disintegrin and metalloproteinase domain-containing protein 10 | Increased expression | Adhesion and proteolysis, dendritic spine formation | Neurons and other cells of the CNS. | Ch15q21.3 |
| *AMZ1/GNA12*[144] | Archaelysin family metallopeptidase 1/Guanine nucleotide-binding protein subunit alpha-12 | Increased expression | Degradation of extracellular matrix proteins/cell differentiation | Neurons and other cells of the CNS. | Ch7p22.3 |
| *APOE3*[165] | Apolipoprotein E3 | Allelic variant | Transports lipids and cholesterol to lymphatics. | Astrocytes, less in microglia and neurons. | Ch19q13.32 |
| *AβPP*[165] | Amyloid beta precursor protein | Increased expression | Binds cell surface proteins, cleaved into defined fragments | Neurons and other cells of the CNS, concentrated in neuronal synapses. | Ch21q21.3 |
| *C9orf72*[166 167] | Chromosome 9 open reading frame 72 | Full or intermediate repeat expansion (20–30 repeats) | Endosomal trafficking, actin regulation, autophagy. | Neuronal cytoplasm, presynaptic terminals. | Ch9p21.2 |
| *C16orf95*[145] | Chromosome 16 Open Reading Frame 95 | Increased expression | Less understood, cellular signalling and regulation, immune response. | Predominantly in microglia, other locations possible. | Ch16q24.2 |
| *CDCA2*[171] | Cell Division Cycle Associated 2 | Decreased expression | Protein targeting during anaphase, alternative splicing, cancer progression. | Regions of neurogenesis (dentate gyrus, subventricular zone). | Ch8p21.2 |
| *CFAP43*[192] | Cilia and Flagella Associated Protein 43 | Nonsense, loss of function C>T | Cilium movement, sperm axoneme assembly and brain development. | Cytoskeleton and cilium axoneme of ependymal cells. | Ch10q25.1 |
| *CWH43*[142] | Cell wall biogenesis protein 43″ | Loss of function deletion | incorporates ceramide into the glycosylphosphatidylinositol anchor in yeast | Apical surface of ependymal cells and choroid plexus. | Ch4p11 |
| *MLLT10*[144] | ALL1-Fused Gene From Chromosome 10 Protein | Decreased expression | Chromatin remodelling and transcriptional regulation. | Neurons and other cells of the CNS. | Ch10p12.31 |
| *SFMBT1*[144] | Scm Like With Four Mbt Domains 1 | Copy number loss of intron 2 | Chromatin modification. | Smooth muscle of and endothelium of vasculature, ependymal cells lining the ventricles and cells of the choroid plexus. | Ch3p21.1 |
| *PLEKHG1*[144] | Pleckstrin Homology Domain-Containing Family G Member 1 | Increased expression | Rho GTPase signalling pathways, actin cytoskeleton organisation. | Neurons, motor control or areas of high cellular turnover and plasticity. | Ch6q25.1 |
| *SLCO1A2*[144] | Solute Carrier Organic Anion Transporter Family Member 1A2 | Decreased expression | Cellular uptake of organic ions | Smooth muscle of and endothelium of vasculature. | Ch12p12.1 |
| *TTR*[165] | Transthyretin | Decreased expression | Transports thyroxine and retinol. | Choroid plexus, retina. | Ch18q12.1 |

CNS, central nervous system; iNPH, idiopathic normal pressure hydrocephalus.

Another gene of interest in amyloid-related pathologies is transthyretin (*TTR*), encoded by the *TTR* gene. An RNA study employing 35 000 probes conducted on 22 iNPH patients and 8 healthy controls revealed a 17-fold reduction in *TTR* expression among individuals with iNPH.[165] *TTR* is well-documented as a marker of neuronal stress, and its expression is upregulated in the rat choroid plexus in response to elevated glucocorticoid levels. Additional genes exhibiting altered expression profiles in iNPH include AβPP, which showed a threefold increase in expression, and *ADAM10*, a protein involved in AβPP proteolysis that also demonstrated increased expression.[166] The differential expression of these genes within the CNS supports the hypothesis that disruptions in amyloid metabolism may contribute to the pathophysiology of iNPH. Nonetheless, a definitive link between genetic variations and the clinical phenotype remains to be established.

**C9orf72:** The recognised functions of the *C9orf72* gene encompass endosomal trafficking and the modulation of actin dynamics.[167] This gene is characterised by mutations involving hexanucleotide repeat expansions, which have been implicated in the pathogenesis of frontotemporal dementia (FTD) and amyotrophic lateral sclerosis.[168] A comprehensive investigation by Korhonen *et al*[168] involving a substantial cohort of potential iNPH patients (n=487) alongside age-matched controls (n=432) identified the presence of the *C9orf72* mutation in 1.6% of the iNPH cohort, while it was absent in the control group. Moreover, mutation carriers exhibited symptomatic onset at an earlier stage than non-carriers. Although the authors advocate for the incorporation of *C9orf72* expansion analysis in patients presenting with iNPH symptoms, the findings of the study are limited by the lack of standardised diagnostic criteria within the iNPH cohort. As a result, the study population may have included individuals with atypical parkinsonism, FTD or other neurodegenerative dementias, potentially confounding the results. Furthermore, one locus encompassing *C16orf95* has been associated with CSF phosphorylated tau levels and lateral ventricular volume in a recent GWAS meta-analysis investigating CSF biomarkers in AD.[169]

CDCA2: The *CDCA2* gene encodes Cell Division Cycle Associated 2 (CDCA2), a nuclear protein integral to chromatin regulation, particularly during the mitotic phase.[170] CDCA2 serves as a critical modulator of chromatin condensation by interacting with Protein Phosphatase 1 (PP1), thereby orchestrating the reorganisation of chromatin post-cell division.[171] Dysregulation of chromatin dynamics, in which CDCA2 is involved, has been implicated in the pathogenesis of various neurodegenerative

diseases, including AD.[172] The interplay between *CDCA2* and broader epigenetic mechanisms in iNPH may also influence the brain's adaptive response to abnormal CSF dynamics, potentially impacting the pathways associated with glymphatic clearance and metabolic waste elimination. Although the precise role of *CDCA2* in iNPH has yet to be fully elucidated, its involvement in chromatin regulation and cellular stability positions it as a promising candidate for contributing to the molecular mechanisms underlying this condition.

***MLLT10*:** The *MLLT10* gene encodes a transcriptional coactivator that plays a pivotal role in chromatin remodelling and gene regulation, primarily through its involvement in the Super Elongation Complex.[173] *MLLT10* is essential for regulating transcriptional elongation, thereby influencing the expression of key genes involved in cell cycle regulation, differentiation and development.[174] In the context of the brain, the proper functioning of *MLLT10* is crucial for maintaining neural progenitor cell activity, which is vital for normal neurogenesis and synaptic plasticity.[175]

In iNPH, *MLLT10* may significantly contribute to the epigenetic regulation of genes that govern neuronal survival, plasticity and responses to injury. Dysregulation of *MLLT10* could lead to impaired chromatin accessibility and transcriptional elongation, potentially resulting in aberrant gene expression profiles in neural cells.[176] Such dysregulation may underlie the cognitive deficits, motor dysfunction and other clinical manifestations observed in iNPH by disrupting the normal maintenance and repair mechanisms within neurons and glial cells.[144] Moreover, *MLLT10* dysfunction could impact genes involved in glymphatic clearance and the removal of metabolic waste from the brain, processes increasingly recognised as compromised in iNPH. Aberrant function of *MLLT10* may contribute to impaired waste clearance, thereby exacerbating neuroinflammation and neuronal stress, which could accelerate neurodegenerative processes.[124] Collectively, these mechanisms highlight the importance of *MLLT10* in maintaining neural homeostasis and underscore its potential role in the pathophysiology of iNPH.

***PLEKHG1*:** The *PLEKHG1* gene encodes Pleckstrin Homology Domain-Containing GTPase Activating Protein 1 (PLEKHG1), a critical regulator of small GTPases, including Rho and Rac.[177] As a guanine nucleotide exchange factor, *PLEKHG1* plays a vital role in modulating the activation of these GTPases, which are integral to various cellular processes such as cytoskeletal reorganisation, cell motility and signal transduction.[177] By facilitating the exchange of GDP for GTP on Rho GTPases, *PLEKHG1* orchestrates key signalling pathways that govern cellular shape, migration and response to extracellular stimuli. Compromised CSF flow and impaired waste clearance in iNPH can lead to neuronal stress and neuroinflammation.[178] *PLEKHG1* may significantly influence the severity of these pathological conditions by impacting cytoskeletal organisation and cell-matrix interactions.[179] Dysregulation of *PLEKHG1* function could exacerbate the adverse effects of altered CSF dynamics on neuronal health, potentially leading to increased cellular stress responses and impaired cellular function. As such, *PLEKHG1* may serve as a pivotal contributor to the neurobiological alterations observed in iNPH, underscoring its potential as a target for therapeutic intervention aimed at mitigating the cellular consequences of this condition.[144] Table 2 summarises the candidate genes identified in an association with iNPH pathophysiology.

There also exists a condition characterised by the early onset of essential tremor (ET) in young adulthood, which evolves into iNPH in later life, referred to as essential tremor idiopathic normal pressure hydrocephalus (ETINPH).[180] A longitudinal study has revealed its genetic basis, identifying a linkage region on chromosome 19q12-13.31 through genome-wide linkage analysis.[181] Several genes within this locus are expressed in the nervous system, offering potential insights into the pathogenesis of both ETINPH and iNPH. Notable genes in this region include ATP1A3 and PSEN2. The ATP1A3 gene encodes the Na+/K+−ATPase pump, with mutations in this gene linked to rapid-onset dystonia-parkinsonism.[182] The PSEN2 gene encodes Presenilin 2, a protein involved in the processing of AβPP, with alterations in amyloid metabolism being well-documented in the pathogenesis of AD.[183] These amyloid-related mechanisms are also hypothesised to contribute to the pathophysiology of iNPH, as described in previous subheadings of this review.

## UP-TO-DATE MULTIFACTORIAL UNDERSTANDING OF NPH PATHOPHYSIOLOGY

### Limitations of the current pathophysiological concepts

Human understanding is often constrained by approximation, limiting the comprehension of complex, multifaceted concepts. In the context of NPH, the Monro-Kellie doctrine, commonly referenced to explain hydrocephalus pathophysiology, requires a nuanced interpretation. While the doctrine traditionally posits a static model, it overlooks the dynamic nature of its components, including CSF, blood and brain tissue. Critically, it does not account for pressure gradients across individual compartments, which are vital for intracranial dynamics. One significant oversight in this static model is the underestimation of the role of cerebral venous drainage, with the focus traditionally placed on arterial inflow. This is problematic because cerebral venous drainage is asymmetric in approximately 50% of individuals.[64] Consequently, venous sinus obstructions affecting the dominant sinus exert far greater effects on ICP than those affecting non-dominant sinuses.[184]

The interaction between CSF and venous pressures is now recognised as more significant than previously assumed, particularly in conditions like idiopathic IIH.[185] Elevated central venous pressure can increase ICP when compensatory mechanisms fail, leading to brain oedema and swelling. This suggests that greater attention should be paid to cerebral venous contributions when evaluating the pathophysiological mechanisms of hydrocephalus, rather than relying solely on the Monro-Kellie doctrine, which may oversimplify these complex dynamics.

Addressing chronic diseases like iNPH presents additional challenges, as most studies involve heterogeneous patient populations presenting with varying symptoms at different stages of disease progression. Current research is fragmented, focusing on individual factors that may be associated with iNPH pathophysiology without fully understanding their interactions or causality. Recent advances in fluid dynamics and genetic research offer promising insights, but comprehensive understanding of the underlying mechanisms will require further investigation.

Moreover, human studies, particularly in the areas of glymphatic drainage and lymphatic outflow, remain limited, with much of the current data derived from animal models. Long-term studies on the disease's natural progression are also scarce. Furthermore, the clinical heterogeneity in diagnosing NPH often leads to misdiagnosis or underdiagnosis, as additional, unrecognised factors may contribute to the disease's pathophysiology. These gaps underscore the need for more critical, integrative research approaches to better elucidate the complex mechanisms driving NPH.

## Definition of the disease

Historically, the classification of NPH has delineated two primary subtypes: (1) iNPH, characterised by an unknown aetiology without any identifiable prior illness or trauma, and (2) secondary NPH (sNPH), which occurs as a consequence of underlying conditions such as neuroinfections, intracranial haemorrhage or traumatic brain injury. Recent advances in genetic and molecular research have led to the recognition of the following additional categories: transition (treated before age 18 years), unrecognised congenital (congenital pattern, not treated before age 18 years), acquired (secondary to known risk factors, treated or untreated) and suspected iNPH.[186] Some authors refer to congenital NPH, which occurs atypically in younger individuals including children, and familial NPH, characterised by a higher prevalence within certain families with identifiable genetic mutations associated with NPH pathogenesis.[139 140 187]

Before a definitive iNPH diagnosis can be made, a systematic evaluation is required to identify candidates for shunt treatment based on the highest level of available evidence. These evaluative stages are classified as suspected, possible and probable iNPH, each reflecting a different degree of diagnostic certainty prior to shunt intervention.[188] Definite iNPH, or shunt-responsive iNPH, is confirmed by an objective improvement in clinical symptoms following shunt surgery.

The distinction between iNPH and sNPH remains a significant diagnostic challenge. The presence of multiple comorbidities and the multifactorial nature of iNPH pathophysiology complicates the clear delineation of these subtypes. This raises the possibility that a substantial number of cases currently classified as idiopathic may in fact represent sNPH. Our limited understanding of the exact pathophysiological mechanisms underlying these conditions further obscures the identification of causative factors, making it difficult to reclassify certain iNPH cases as sNPH. As research progresses, it is conceivable that many cases presently categorised as idiopathic may ultimately be redefined as secondary on the discovery of distinct etiological factors.

Currently, clinical and radiological markers for NPH are not entirely specific. Classification systems focus on the most common features, primarily aimed at defining iNPH, but many patients fall into a diagnostic 'grey zone', where clinical certainty remains suboptimal due to the lack of a standardised diagnostic framework. This lack of specificity, both in clinical presentation and imaging, complicates the achievement of a definitive diagnosis, contributing to diagnostic ambiguity in many cases.

This complexity is also evident in research on NPH, where studies frequently identify various correlating factors related to disease differentiation, shunt responsiveness, optimal diagnostic techniques and levels of clinical improvement. However, the ability to determine which factors most significantly influence NPH pathophysiology across different stages of disease progression remains elusive. As a result, current research is often focused on identifying correlations rather than establishing causal relationships. This highlights the necessity for further investigations to elucidate the precise mechanisms driving NPH and to advance understanding of its aetiology and progression.

An additional condition of interest is asymptomatic ventriculomegaly with features of iNPH on MRI (AVIM).[189] A pioneering Japanese study followed eight asymptomatic subjects over a period of 4≥8 years, two of whom developed dementia and/or gait disturbances, with one showing worsening ventriculomegaly on MRI. The prevalence of probable iNPH in individuals over the age of 61 in Japan was found to be 0.51%. In 2020, the same research group[190] expanded these findings in a multicentre study involving 93 participants with AVIM. 52 participants were followed for 3 years, during which 52% progressed to iNPH—11 classified as definite, 6 as probable and 10 as possible. The remaining 25 participants remained asymptomatic. The study concluded that the progression rate from AVIM to iNPH was approximately 17% per year. AVIM may thus represent a preclinical stage of iNPH, and its presence should be considered during clinical MRI evaluations. Notably, baseline iNPH Grading Scale scores were found to be predictive of AVIM-to-iNPH progression (p=0.002).

## OVERVIEW AND SUMMARY

- Ventricular enlargement in iNPH is primarily caused by the accumulation of CSF due to delayed outflow through the ventricular system, leading to increased mechanical stress on periventricular white matter.
- The chronic nature of iNPH is exacerbated by age-related brain atrophy, which further damages the ependymal lining of the ventricles, resulting in decreased compliance and a 'stiff ventricle' state.
- Impaired CBF is a significant factor in iNPH pathophysiology, with altered perfusion characteristics correlating with cognitive decline in affected patients.
- The interplay between CSF dynamics and fluid interchange between the BBB and ISF is critical in understanding the pathophysiological changes associated with iNPH.
- The accumulation of ISF can lead to increased transmantle pressure, resulting in further obstruction of CSF circulation and exacerbating neuronal injury.
- Oxidative stress contributes to small artery spasm and thrombosis, leading to cortical ischaemia and reduced potential for remyelination in iNPH patients.
- Astrocytic reactivity, marked by increased TNF-alpha production, is linked to neuronal dysfunction and cognitive decline in iNPH.
- Glymphatic system impairment in iNPH likely disrupts the clearance of ISF and metabolites, further contributing to cognitive decline and neurodegenerative processes.
- Dysfunction of motile cilia on ependymal cells may impair coordinated CSF flow through the ventricular system, while abnormalities in primary (non-motile) cilia, which act as cellular mechanosensors, can disrupt signalling pathways essential for ventricular development and CSF homeostasis. Emerging evidence suggests that ciliary defects contribute to ventricular enlargement and impaired CSF circulation in iNPH.
- Genetic factors may play a role in the susceptibility to iNPH, although the specific genes involved remain largely unidentified, necessitating further research to understand the hereditary contributions to the condition.

## CONCLUSIONS

The pathophysiology of NPH represents a complex convergence of neuroanatomical changes, disrupted CSF circulation and biochemical imbalances, culminating in characteristic symptoms of gait disturbances, cognitive deficits and urinary incontinence. Ventriculomegaly, largely driven by compromised CSF drainage and glymphatic system dysfunction, places significant mechanical pressure on adjacent periventricular white matter, resulting in neuronal damage and progressive functional impairment. It is imperative to emphasise the importance of targeted inquiries into the interplay between genetic predispositions, glymphatic system dysfunction and the definitional challenges associated

with this disorder, as these elements are crucial for elucidating the pathophysiological underpinnings of iNPH. Research should prioritise the simultaneous exploration of multiple contributory factors to the disease's pathogenesis, rather than examining these elements in isolation, to ascertain causative relationships instead of correlations. By focusing on these fundamental aspects, the scientific community can facilitate the development of more precise diagnostic frameworks and therapeutic modalities, thereby optimising patient outcomes and addressing the urgent concerns posed by an ageing population increasingly susceptible to this neurodegenerative disorder.

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