BMJ Neurology Open

Review of theories into the pathogenesis of normal pressure hydrocephalus

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To cite: Mani R, Basem J, Yang L, *et al*. Review of theories into the pathogenesis of normal pressure hydrocephalus. *BMJ Neurology Open* 2024;**6**:e000804. doi:10.1136/bmjno-2024-000804

Received 19 June 2024
Accepted 01 September 2024

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ABSTRACT

Normal pressure hydrocephalus (NPH) represents a unique form of hydrocephalus characterised by the paradox of ventriculomegaly without significant elevations in intracranial pressure, with the clinical triad of gait instability, cognitive impairment, and urinary incontinence. A myriad of neurobiological correlates have been implicated in its pathophysiology. We review the literature to provide an up-to-date, narrative review of the proposed mechanisms underlying the pathophysiology of NPH, proposing a holistic framework through which to understand the condition.

We conducted a narrative review of the literature on NPH, assessing the various mechanisms underlying its pathophysiology and clinical presentation.

NPH represents a unique form of hydrocephalus manifesting as a disorder of the cerebral vasculature, characterised by arteriosclerosis and reduced intracranial elastance. There are multiple mechanisms underlying its pathophysiology, which include windkessel impairment causing redistribution of intracranial pulsatility from the subarachnoid space to the ventricles, reductions in cerebral blood flow, impaired glymphatic clearance, reduced blood–brain barrier integrity and alterations in venous haemodynamics. Moreover, NPH shares similar clinical features and pathological mechanisms as other neurodegenerative conditions such as Alzheimer's disease and vascular dementia. The severity of each respective mechanism of pathophysiology can lead a patient to develop one condition versus another.

Analysing NPH as a disorder of the cerebral vasculature, glymphatics, and most of all, the distribution of intracranial pulsatility, provides a novel framework through which to understand and manage this condition, one which requires further investigation.

INTRODUCTION

Normal pressure hydrocephalus (NPH) is characterised by the clinical triad of gait disturbance, cognitive impairment and urinary incontinence and differs from other forms of hydrocephalus in that it is characterised by ventriculomegaly without a significant increase in intracranial pressure (ICP). This paradoxical condition was first described in detail in 1965 by Adams *et al*, who described patients over 60 years of age with a progressive history of forgetfulness with slowness of thought, unsteady shuffling gait and urinary incontinence.[1] After ruling out other metabolic or infectious causes, these patients underwent pneumoencephalograms which demonstrated diffuse ventricular dilatation of their ventricular systems. These patients had no prior history of meningitis, traumatic brain injury or subarachnoid haemorrhage (SAH), with cerebrospinal fluid (CSF) pressure consistently below 180–200 mm H_2O.[1] Adams *et al* opted to treat these patients via surgical shunting and noted 'the rapid restitution of the patients' health' after shunting.[1] The authors also noted that one patient, after falling and disconnecting their shunt hardware, returned to the hydrocephalic state.[1]

Since then, NPH has been diagnosed in elderly patients in the setting of clinical progression of various combinations of the three symptoms above (primarily gait disturbance).[2 3] This is coupled with radiographic evidence of diffuse ventricular dilatation (an Evans' index >0.3) out of proportion to cerebral atrophy without signs of macroscopic obstruction or other organic causes of hydrocephalus (SAH, intracranial lesions, meningitis and trauma).[3] Other radiographic features suggestive of NPH include temporal horn dilatation not accounted for by hippocampal atrophy, a callosal angle <90°, bowing of the corpus callosum, narrowing of the posterior half of the cingulate sulcus (cingulate sulcus sign), disproportionate crowding of gyri near the convexity[4] and dilated Sylvian fissures with focal dilation of sulci (transport sulci), referred to as 'disproportionately enlarged subarachnoid space hydrocephalus'.[2 3] Figure 1 demonstrates an NPH patient at our institution with characteristic radiographic findings.

Confirmatory testing includes lumbar puncture (LP), with normal opening pressures (5–18 mm Hg), with an improvement in symptoms following large volume LPs (tap test) highly suggestive of the diagnosis.[2 3]

The definitive treatment for NPH patients is CSF diversion via shunt placement, with

subsequent symptomatic improvement noted in up to 84% of patients.[2 3] This improvement in clinical symptoms from shunting, particularly gait and cognitive symptoms, allows for differentiation from other progressive conditions with similar presentations, such as Alzheimer's disease (AD), Parkinson's disease (PD) and Binswanger's disease. These clinical improvements can be sustained for years following shunt placement, with gait demonstrating the most marked and sustained symptomatic improvement for 75%–87% of patients.[5] Even for NPH patients requiring shunt revision for shunt malfunction or infection, 74%–93% of patients in the literature have demonstrated long-term improvements in symptomatology following revision surgery.[5]

The underlying pathophysiology of NPH has been of great interest over the years, with various theories presented to account for the underpinnings of its peculiar clinical presentation. While various theories have been proposed since Adams *et al's* findings to account for the symptomatology and pathophysiology of NPH, a definitive theory of pathogenesis is still lacking. We believe that this stumbling block in understanding the pathophysiology of NPH stems from the larger issue that the existing paradigm of the Monro-Kellie pressure-volume model, from which our fundamental understanding of hydrocephalus is derived,[6] insufficiently accounts for many of the clinical and experimental characteristics associated with different forms of hydrocephalus. There are a myriad of biological processes implicated in NPH, ranging from arteriosclerosis,[7 8] and impaired blood flow,[9] to impairments in the glymphatic pathway,[10] to disturbances in the distribution of intracranial pulsatility.[11 12] In this manuscript, we review the various underlying pathophysiological mechanisms underlying NPH and attempt to amalgamate these mechanisms to account for the clinical and radiographic manifestations of this condition.

METHODS

We conducted a narrative review of literature discussing the pathophysiology of NPH in October 2023 and in March 2024 via electronic databases (PubMed and Medline). With the growing perspective of hydrocephalus as a disorder of intracranial pulse redistribution in the hydrocephalus community,[11 12] we started our review within this framework of NPH as a disorder of intracranial pulsatility. We applied the search terms "normal pressure hydrocephalus", "NPH", "NPH pathogenesis", "intracranial pulsatility" and "hydrocephalus" to the search engines of these databases. We included the following categories of articles: systematic and narrative reviews, neuroimaging studies, neuropathological studies, research articles exploring the physiology of hydrocephalus, animal models of hydrocephalus and reports on surgical treatment. Non-English language articles, single-patient case reports, editorials and commentaries were excluded from the review. During the review of articles exploring intracranial pulsatility in NPH, we also sought to determine which other pathophysiological mechanisms were cited in the literature. We reviewed the list of references cited by articles analysing intracranial pulsatility in NPH which also presented other pathophysiological mechanisms implicated in NPH. We included references either cited by at least 200 articles or for which there were at least 5 related articles exploring each pathophysiological process. This yielded four other mechanisms implicated in NPH: glymphatic drainage, blood–brain barrier (BBB) integrity, cerebral blood flow (CBF) impairment and venous haemodynamics. Following our initial literature review, after detecting patterns of similar pathophysiology between AD and NPH, we also applied the search terms "NPH and dementia" and "pathophysiology of dementia".

In total, we reviewed 80 substantive articles that explored the clinical and radiographic characteristics of NPH, various pathophysiological mechanisms implicated in the condition, and articles demonstrating similarities

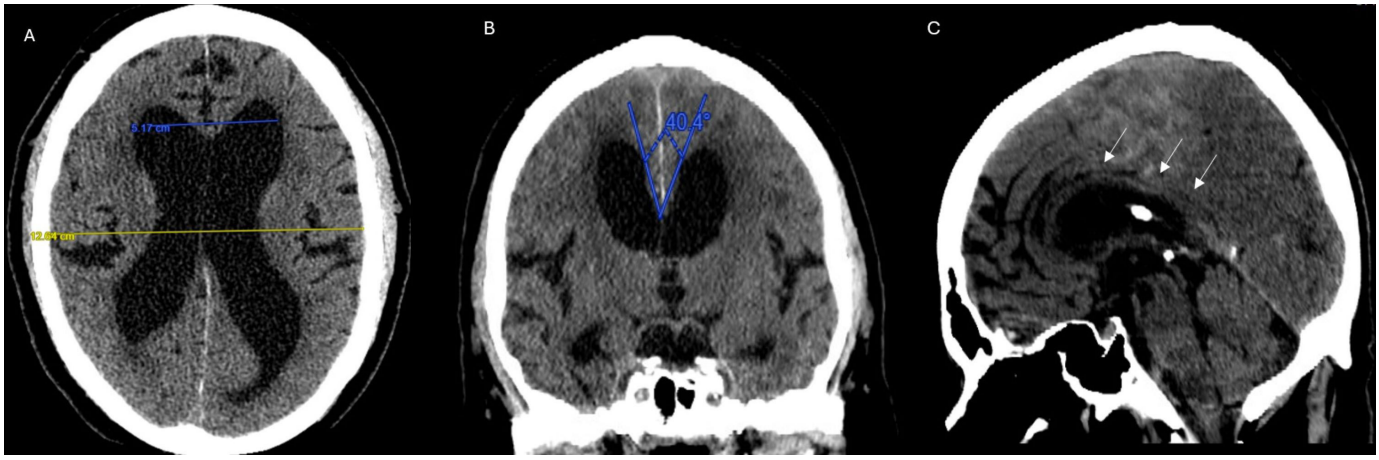

Figure 1 Demonstration of radiographic features of NPH. (A) Axial CT head demonstrating Evans index of 0.44; (B) Coronal CT head demonstrating acute callosal angle of 40.4° with DESH; (C) Sagittal CT head demonstrating cingulate sulcus sign (white arrows). DESH, disproportionately enlarged subarachnoid space hydrocephalus; NPH, normal pressure hydrocephalus.

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in pathophysiology between NPH and other neurodegenerative conditions and cited 40 articles that thoroughly address the critical mechanisms outlined below.

DISCUSSION

Proposed theories of pathogenesis

Adams *et al* posited that the apparent paradox of ventriculomegaly with normal ICP could be explained by a 'hydraulic-press mechanism'. In accordance with Pascal's law of hydrodynamics, this theory states that the force exerted on the ventricular walls is the product of the CSF pressure and the ventricular area. The authors proposed that there is an initial, transient state of elevated ICP and the ventricular dilatation seen in NPH serves to increase the surface area for CSF absorption, with a commensurate decrease in CSF pressure to a 'normal' level, such that the product of ventricular surface area and pressure remains constant.[1]

Adams *et al* also proposed that the ventricular dilatation seen in NPH caused stretching of adjacent white matter tracts which may account for its clinical symptoms.[1] However, these proposed mechanisms raise further questions. First, other forms of hydrocephalus, such as obstructive hydrocephalus (OH), are also characterised by ventriculomegaly which may also stretch these white matter tracts. However, these hydrocephalic conditions do not typically present with Hakim's triad that characterises NPH.[12] Second, these forms of hydrocephalus are characterised by persistent elevations in ICP even in the setting of ventriculomegaly, which raises the question as to why the 'hydraulic press mechanism' would be unique to NPH. Furthermore, the responsiveness to CSF diversion is varied, and the extent of reduction in ventricular dilatation has not been demonstrated to correlate with improvement in symptomatology. Even patients with significant clinical improvement to resolution have demonstrated only a 10% reduction in Evans' index.[4] Moreover, ventricular size and volume have not definitively been shown to correlate with the severity of disease even prior to shunting.[4]

Significant research has been done to explore various pathological mechanisms to account for this condition. Generally, intracranial dynamics with respect to hydrocephalus have traditionally been analysed within the framework of the Monro-Kellie doctrine.[6] This states that the cranium contains three nearly incompressible substances—brain, blood and CSF—and any change in one variable must be accompanied by a commensurate change in the other(s), based on the principle of mass conservation.[6] In this framework, hydrocephalus is understood to be a disorder of 'bulk flow' of CSF, with an imbalance between the formation and reabsorption of CSF. This would result in the 'back up' and accumulation of CSF, and subsequent ventricular dilatation with increased ICP. However, in NPH, characterised as a form of 'communicating' hydrocephalus, there is no obstructive lesion affecting CSF outflow, nor is there a lesion affecting CSF reabsorption. Moreover, if obstruction occurred at the arachnoid villi, where CSF has been purported to undergo reabsorption, then the temporal sequence would involve downstream dilation which works its way proximally, that is, dilation of the subarachnoid spaces (SAS) prior to ventricular dilatation, which does not manifest in conditions of hydrocephalus, let alone NPH. Moreover, our understanding of hydrocephalus as a disorder of CSF absorption depends on the validity of the traditional model of CSF bulk flow dynamics. Research over the past few decades has shown that CSF is not absorbed in the arachnoid villi at normal ICP, but rather along the arachnoid sleeves of the cranial nerves and possibly at the brain capillaries.[13] The complexity and ubiquity of CSF absorptive sites make the theory that hydrocephalus is due to impaired CSF absorption less credible. Therefore, this 'bulk flow' model is inadequate in accounting for the pathophysiology of NPH.

Recent theories have pointed towards this condition being a disorder of intracranial vasculature. For instance, NPH has been characterised in the literature by intracranial arteriosclerosis.[7 8] Similarly, several studies have noted ischaemic changes due to reduced CBF in the deep white matter of NPH patients, ranging from the periventricular white matter to deep white matter regions between the middle cerebral artery perforators and the deep medullary pial branches.[7 8 14]

Moreover, there is substantive literature analysing forms of hydrocephalus as disorders of intracranial pulsatility. Rather than the 'back up' of CSF, it is the redistribution of pulsations delivered through the cardiac cycle from the SAS to the ventricles that is implicated in the pathophysiology of hydrocephalic conditions, such as NPH.[15]

Impairments in the glymphatic system have also been implicated in NPH.[10] This system serves as a 'waste clearance' system from the parenchyma.[10] This is potentially due to loss of arterial compliance and reductions in expression of aquaporin-4 (AQP4) channels, leading to accumulation of waste products and possible neurotoxicity, akin to amyloid-beta (Aβ) accumulation in AD.[10 16] Also related to the accumulation of proteins is the dysfunction of the BBB, which has also been noted in NPH, leading to increased permeability to proteins and impairments of CSF circulation and clearance.[17]

There are multiple, concurrent pathophysiological processes in NPH. Furthermore, these disease processes overlap with other neurodegenerative conditions such as AD (with accumulation of toxic proteins) and Binswanger's disease (arteriosclerosis), both of which are part of the differential diagnosis for patients with this constellation of symptoms. We believe that these conditions each exist on a spectrum, and the extent of perturbation of each respective pathological process leads towards one condition versus the other. Below, we review the following pathophysiological mechanisms in detail:

1. Impairments in CBF.
2. Redistribution of intracranial pulsatility.
3. Alterations in venous haemodynamics.

4. Reduced glymphatic clearance.
5. Compromised BBB integrity.

We discuss how to incorporate these processes to provide a thorough understanding of the disease process and a better understanding of the condition with respect to other neurodegenerative diseases.

Impairments in CBF

The view of NPH as a cerebrovascular disorder stems from findings of both global and focal areas of CBF reduction in the frontal cortex, periventricular white matter, the cingulate gyrus and in deeper structures such as the thalamus, hippocampus and lentiform nucleus compared with healthy age-matched controls.[9 18] This alteration in CBF has been demonstrated as hyperintensities on T2-weighted MRI, as well as with increased levels of lactate accumulation in the areas listed above.[18] Furthermore, the literature has shown that NPH patients tend to exhibit arteriosclerosis in their cranial vasculature, with various postmortem pathology studies of NPH patients demonstrating arteriosclerotic vasculopathy with multiple lacunar infarcts in the periventricular white matter, but with normal arachnoid villi and leptomeninges. Retrospective analyses show that these NPH patients often had risk factors for hypertensive cerebrovascular disease.[7 8]

Various studies have also demonstrated correlations between reductions in CBF in the various regions above and clinical symptomatology, particularly worsening gait.[19] However, global areas of hypoperfusion have also been cited in the literature, making definitive localisation of areas of ischaemia to specific clinical symptomatology inconsistent and difficult.[9]

These CBF reductions in NPH patients have been measured prior to and following shunt placement. Studies show that preoperative CBF reduction in shunt-responsive patients correlates with the severity of their NPH symptoms.[19] Others have found that clinical improvements following CSF drainage via shunting also correlate with restoration of CBF, which itself correlates with reduced ventriculomegaly and periventricular lucencies.[19] Additionally, CBF values in some NPH patients improve following CSF removal, even via LP, a finding not noted in patients simply with age-related atrophic changes.[20]

In correlating ischaemia to the underlying clinical and radiographic presentation of NPH, some authors have posited an impairment in autoregulation, particularly in the periventricular white matter due to increased periventricular CSF diffusion, which may improve following CSF diversion.[19] Reductions in CBF and impaired vasomotor responses during 5% carbon dioxide and 100% oxygen inhalation have been noted, with improvement in these autoregulatory impairments following CSF diversion via LP or shunting.[21]

As for investigating the causal relationship between ischaemic changes and ventricular dilatation in NPH, investigators have proposed that there is compression of the deep vasculature with stretching of the anterior cerebral artery by the dilated ventricles, which reduces flow and may lead to these ischaemic changes.[20] Others have proposed the reverse that vascular disease and ischaemic changes may lead to ventricular dilatation as the resulting ischaemia leads to damage to the white matter and resulting tissue loss.[14 20]

Other studies have refuted a correlation between CBF and NPH, with not all NPH patients demonstrating significant impairments in CBF or autoregulatory capacity.[14] Moreover, the underlying mechanism by which CBF may improve following shunting in shunt-responsive patients is still unclear.[3] Therefore, while CBF impairment is common and may partially contribute to its clinical presentation, it does not sufficiently account for the clinical and radiographic manifestations of NPH.

Redistribution of intracranial pulsatility

Given the shortcomings of the 'bulk flow' model in accounting for the phenomena in NPH, another approach to NPH and hydrocephalus, in general, has been through the framework of intracranial pulsatility.[12 22 23] Experimental evidence has demonstrated that hyperdynamic choroid plexus pulsations are necessary and sufficient for ventricular dilation in communicating hydrocephalus, even without an obstruction to CSF flow.[22–24] For instance, unilateral choroid plexectomy led to the prevention of dilation of the ipsilateral ventricle but not the other, whereas, intraventricular saline infusions (to simulate bulk flow and accumulation of CSF) did not induce ventriculomegaly.[15 24] Other authors have noted that communicating hydrocephalus may be induced by increasing the amplitude of the intraventricular pulse pressure even while keeping the mean CSF pressure and absorption constant.[22] Conversely, interruption of flow from the anterior choroidal artery has been shown to prevent dilatation of the ipsilateral ventricle.[24]

Physiologically, these pulsations are delivered to the cranium during the cardiac cycle via the arteries. This arterial blood pressure pulse is dampened in the cranium, by transmitting this pulse from arteries to veins via the CSF pathway, bypassing the microvasculature to render capillary flow smooth.[11 12] This pulsatile CSF flow has been demonstrated in flow MRI studies, showing that pulsatile arterial, CSF and venous flow are normally synchronous throughout the cardiac cycle.[23] The CSF path, therefore, has been posited to serve as a hydraulic link of arterial expansion and relaxation to venous compression and re-expansion. This has been proposed as the 'cerebral windkessel' mechanism.[12] Therefore, perturbations to the mechanism above which may lead to redistribution of that pulse pressure may be implicated in various forms of hydrocephalus, including NPH.

Flow MRI has demonstrated marked increases in ventricular CSF pulsatility in clinical hydrocephalus, accompanied by diminished pulsatility in the SAS.[25] Greitz described this pattern of pulsatility characteristic of hydrocephalus as redistribution of pulsatility from the SAS to the ventricles.[25] Therefore, hydrocephalus can be understood as a manifestation of increased impedance to

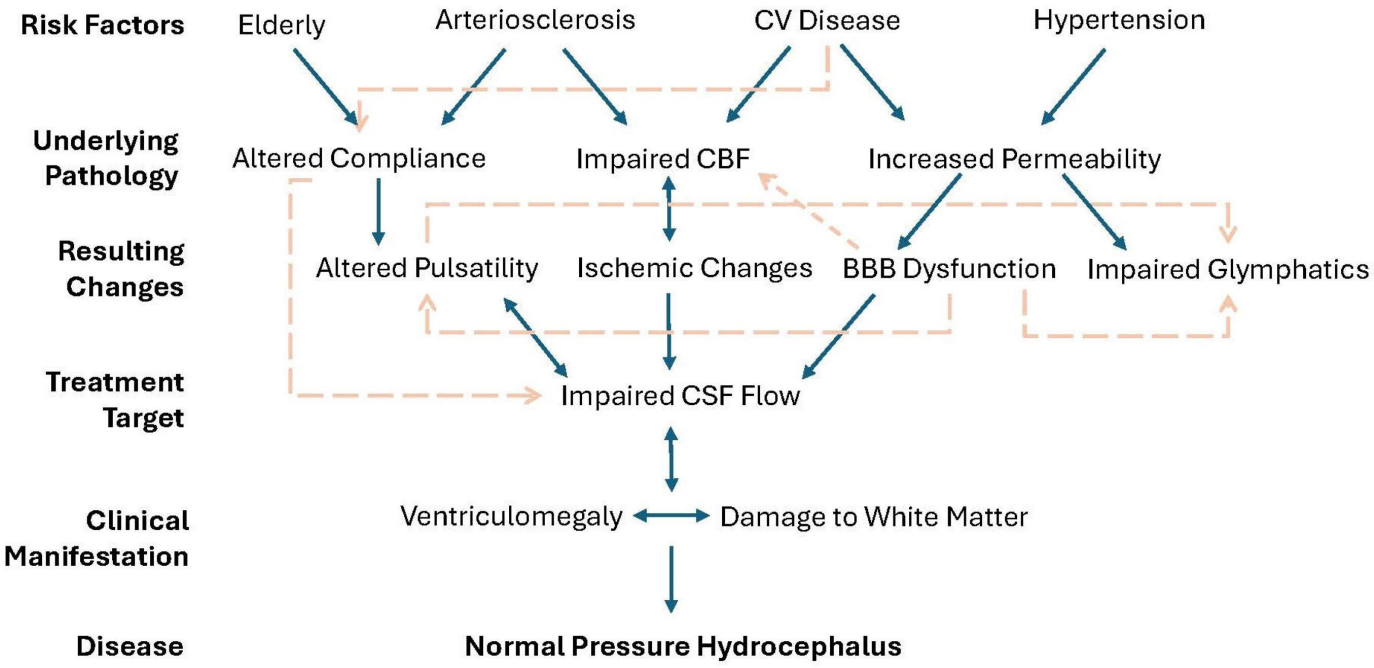

Figure 2 The various mechanisms underlying the pathophysiology of NPH. BBB, blood–brain barrier; CBF, cerebral blood flow; CSF, cerebrospinal fluid; CV, cerebrovascular.

the flow of CSF pulsations in the SAS, with redistribution of the flow of pulsations into the ventricular CSF and into the capillary and venous circulation.

Egnor *et al* have proposed that cerebral windkessel dysfunction accounts for the clinical and radiographic features of NPH.[11 12] They proposed that various forms of hydrocephalus are due to impairments of windkessel effectiveness. Windkessel effectiveness is given by the CSF path inertance multiplied by CSF path elastance divided by CSF path resistance. Windkessel impairment can be due to increased impedance due to increased resistance in the CSF spaces to CSF pulsations (OH) or to increased impedance in the CSF spaces due to decreased inertance (arteriosclerosis) and decreased elastance (brain atrophy).[12]

When the windkessel is physiologically tuned, the windkessel effectiveness (W) is given by

$W=IK/R$

where I is the CSF path inertance (ie, pulse magnitude), K is CSF path elastance and R is resistance in the CSF path and the damping in the brain parenchyma.

This is relevant to NPH for the following: in NPH, there is a combination of arteriosclerosis (which the authors note blunts the CSF pulse in the SAS—lowering I in the windkessel equation) and age-related softening of brain tissue as noted by findings from MR elastography) (which decreases the elastance of subarachnoid CSF pathways—lowering K in the windkessel equation).[12] These perturbations reduce the effectiveness of the windkessel in NPH. In NPH (and other forms of hydrocephalus), ventricular dilatation may represent an adaptive response which decreases resistance to CSF pulsations via increasing the radius of the CSF path. This would thereby increase the volume of available CSF for coupling of arterial to venous pulsations. The authors, therefore, propose that ventriculomegaly is an active response to mitigate windkessel impairment, not a passive process.[12]

The authors note that the form of windkessel impairment in NPH (related to impairments in compliance and inertance) differs from OH (related to increased resistance in the CSF path), which accounts for why NPH is less deleterious clinically than OH.[12]

In NPH, the windkessel is still able to function as it is not 'glued' by high resistance, but it functions at the cost of an elevated ventricular pulse amplitude which exerts stress on the periventricular leg and bladder fibres, which may account for the symptomatology seen in NPH.[12]

Egnor *et al* also propose that CSF diversion via shunting provides a long-term means of lowering resistance in this CSF path by providing an additional conduit for this pulsatility. Shunting, therefore, provides an accessory windkessel, thus lowering the need for adaptive ventriculomegaly.[12]

Alterations in venous haemodynamics

While arterial pathophysiology has been implicated in NPH, others, particularly Bateman, have also noted the role of alterations in venous haemodynamics in this condition. Greitz *et al* had initially posited in 1997 that communicating hydrocephalus was caused by impairments of arterial pulsation and that OH manifested largely due to compression of cortical veins.[26] However, Bateman noted that this theory did not sufficiently account for venous compression which he notes does manifest in all forms of hydrocephalus, including communicating hydrocephalus.[27] Bateman notes experimental evidence that, in NPH patients, venous compliance in the superior sagittal sinus (SSS) was reduced compared with healthy individuals

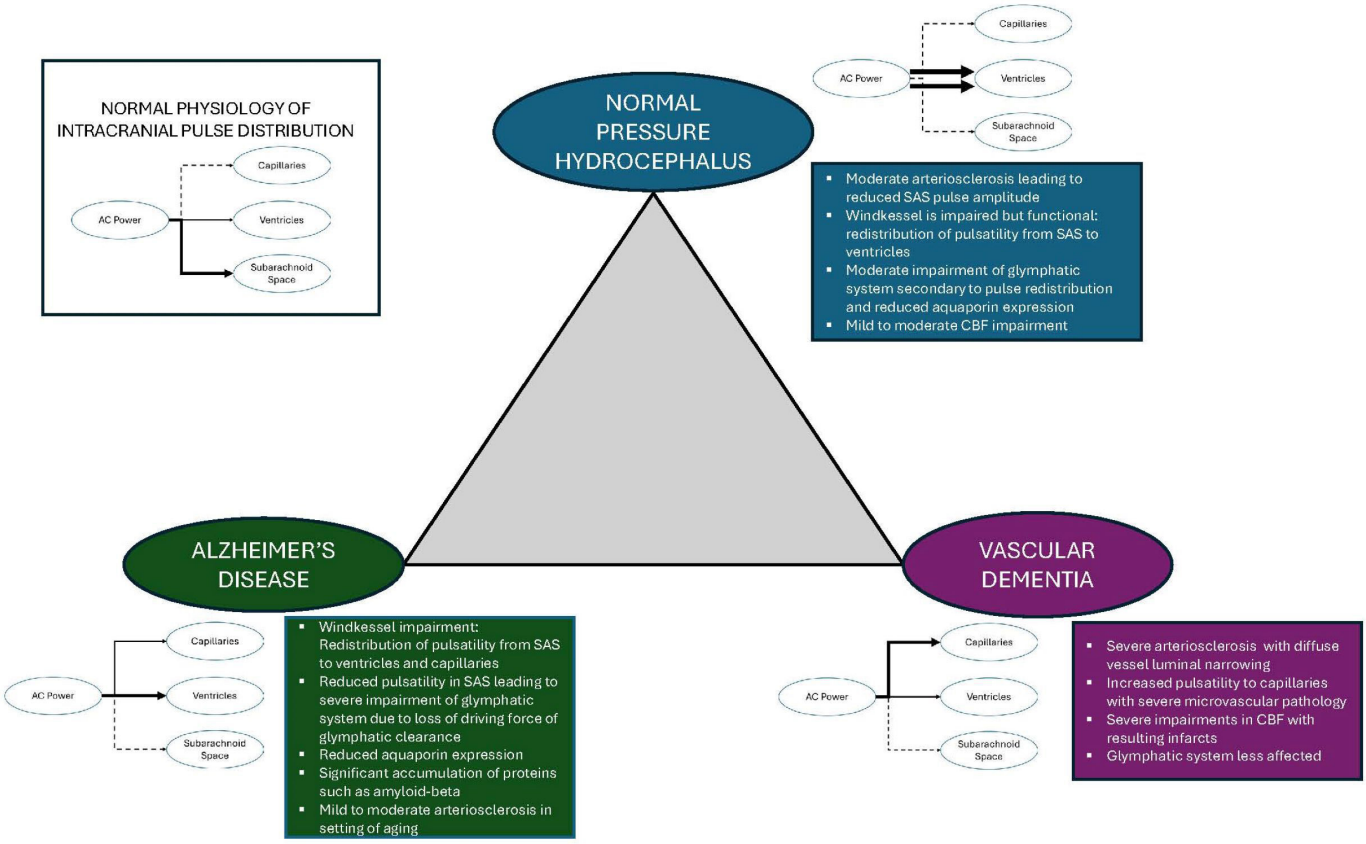

Figure 3 This schematic representation illustrates the spectrum of NPH, Alzheimer's disease and vascular dementia, outlining the relevant pathophysiology that characterises and predominates in each condition. It also demonstrates the normal physiology of intracranial pulsatility and the pathological redistribution of the intracranial pulse that we propose for each condition. CBF, cerebral blood flow; NPH, normal pressure hydrocephalus; SAS, subarachnoid space.

and patients with ischaemia and atrophic changes. This reduction in compliance improved following intervention via CSF diversion in patients with corresponding clinical improvement, with improvements in blood flow to the SSS following shunting.[14] Bateman cites a reduction specifically in superficial venous drainage in NPH, as these findings were not noted in the deep venous sinuses.[27]

Bateman notes that this observed reduction in superficial venous compliance in NPH patients may provide insight into the pathophysiology of NPH. He notes that ageing leads to a reduction in craniospinal compliance, with a resulting elevation in superficial venous pressure.[14] This increase in venous pressure leads to subsequent stiffening of the cortical veins which further propagates a worsening in venous vascular compliance in a 'positive feedback loop'.[14] This subsequently compromises the pressure gradient otherwise required to reabsorb CSF, thereby leading to reduction in CSF absorption.[14] Additionally, this reduced venous compliance potentially has an effect upstream on the propagation of the intracranial pulse, by reducing arterial expansion in the SAS and leading to the propagation of the pulse to the microvasculature and parenchyma.[14]

Bateman has also posited that the ventricular dilatation seen in NPH may be due to the redistribution of this vascular pulsation in the setting of venous compression. This leads to an intraventricular 'water-hammer' pulse which may elicit shear stress leading to parenchymal atrophy, as has been implicated in conditions such as dementia and normal age-related atrophy.[27] He proposed that this may lead to an outward bowing of the ventricles and the subsequent dilatation seen on imaging for NPH patients.[27]

Reduced glymphatic clearance

The glymphatic system (a portmanteau of 'glia' and 'lymphatic') is a newer concept of waste clearance by the cranium. It is defined as using CSF flow to connect perivascular spaces to venous drainage and interstitial fluid to clear metabolites, toxins and waste products within the cranium.[28] CSF in the SAS is transmitted via arterial pulsations and enters the interstitial space via AQP4 transporters found in the astrocytic foot processes. This CSF then travels through the interstitial space and is ultimately removed from the cranium via perineural and perivenous channels.[4 28] This process has been demonstrated to be enhanced during, and dependent on slow-wave sleep.[29]

Perturbations of this glymphatic system have been implicated in various neurodegenerative conditions due to the accumulation of products such as Aβ and hyperphosphorylated tau protein (as seen in AD).[29 30] Reductions

in AQP4 expression in the astrocytic foot processes have been observed in brain tissue from both AD and NPH patients.[16 30 31]

Specific to NPH, radiographic studies have demonstrated impaired glymphatic flow in NPH patients, as noted by decreased clearance of intrathecal gadolinium from the SAS when compared with younger patients being evaluated for intracranial hypotension.[10]

Alterations in the cerebral arterial pulsatility due to age-related stiffening of the vasculature coupled with arteriosclerosis have been implicated in this impairment in glymphatic drainage. Iliff *et al* noted that arterial pulsations are ultimately what drives the paravascular CSF-interstitial fluid exchange of the glymphatic system.[28 32] They noted that dobutamine (an adrenergic agonist) augmented this intracranial pulsatility, which corresponded to an increase in the rate of CSF-interstitial fluid exchange.[28 32] Conversely, unilateral ligation of the internal carotid artery reduced this pulsatility and slowed the rate of CSF-interstitial fluid exchange.[28 32] Without this pulse to drive the glymphatic flow, there is an increased susceptibility to the accumulation of proteins, toxins and waste products. This may account for the cognitive symptoms seen in NPH, which overlap with patients with AD who also share this similar pathophysiology of abnormal accumulation of protein.[29]

Moreover, this impairment in glymphatic flow has been implicated in experimentally observed retrograde aqueductal flow in NPH patients, which reverts to anterograde flow following CSF diversion via shunting.[10] Shunting, therefore, has also been interpreted as providing another conduit to bypass the impairments in glymphatic drainage, and this may account, in part, for the improvement in cognitive symptoms following CSF diversion.[10]

Therefore, the combination of reduced arterial pulsatility and reduced expression of AQP4 in NPH patients has implicated glymphatic impairment as being part of the complex pathophysiology of this condition.

Compromised BBB integrity

The BBB consists of endothelial tight junctions, astrocyte foot processes and pericytes and serves as a selective barrier to maintain a homoeostatic, metabolic milieu for the CNS, through which critical metabolites can enter the CNS while also preventing potentially neurotoxic bloodborne substances from entering.[33] Therefore, any perturbation of this BBB may introduce pathological changes in the CNS with subsequent neurological dysfunction, as has been implicated in various neurological disorders such as ischaemic stroke, epilepsy and AD.[33]

With respect to NPH, the reduced expression of aquaporins in the astrocytic foot processes represents one such perturbation to the BBB as outlined above.[30 31] Moreover, authors have noted a high prevalence of degenerated pericytes in biopsies of NPH patients, which may account for increased BBB leakage.[34] This has been further corroborated by Eide and Hansson, who noted a significantly higher rate of extravasation of fibrinogen, a higher molecular weight protein otherwise not present in normal adult parenchyma, in NPH patients than normal control patients.[35]

The subsequent questions would be why and how BBB dysfunction may be implicated in NPH pathophysiology. The elevation in fibrinogen noted experimentally in NPH patients has been correlated with increased astrogliosis, which may subsequently decrease vascular compliance and further compromise the intracranial dynamics of intracranial pulsatility as outlined above.[35] Additionally, pericytes have been experimentally demonstrated to regulate expression of aquaporins, and their degeneration may contribute, in part, to impairments in the glymphatic system.[35] Pericytes have also been shown to regulate blood flow in the cerebral vasculature, as well as promote erythrogenesis in states of hypoxia, and their compromise may induce hypoperfusion and ischaemic changes, thus contributing to the impairments of CBF also noted in this condition.[35]

Therefore, BBB dysfunction may also provide, in part, a mechanism through which the various pathological processes outlined above may contribute to NPH. It is an avenue that requires further investigation.

Putting it all together

NPH can, therefore, be seen as a clinical manifestation of multiple pathophysiological processes, ranging from impairments in CBF, to impaired vascular and arterial compliance, to cerebral windkessel impairment causing pathological redistribution of intracranial pulsatility, to impairments of glymphatic flow and BBB function. Various combinations of the above mechanisms may be involved in the development of this condition. We demonstrate a schematic of these mechanisms in the development of NPH in figure 2.

NPH on a spectrum of neurodegenerative disorders

The mechanisms noted above are also shared by various neurodegenerative disorders such as AD and vascular dementia (Binswanger's disease), conditions which also overlap with the clinical presentation of NPH (gait instability, cognitive impairment and urinary incontinence).

AD and NPH both share similar pathophysiology through impairments in glymphatic clearance. The accumulation of toxic metabolites from impaired glymphatic clearance is largely due to perturbations in the distribution of intracranial pulsatility, a force that drives the paravascular CSF-interstitial fluid exchange of the glymphatic system. While the redistribution of the pulsatility from the SAS to the ventricles in NPH has been discussed, AD is also characterised by perturbations in intracranial pulsatility. Investigators have noted increased pulsatility indices in the cerebral vasculature in patients with AD.[36] Moreover, postmortem histopathological investigations have demonstrated arteriolar kinking in patients with AD, suggestive of higher pulsatile stress in the microvasculature.[37] Therefore, within the framework of the cerebral windkessel mechanism above, these findings in the

microvasculature of patients with AD may suggest windkessel impairment with redistribution of the pulsatility to the capillaries to a greater degree in AD than NPH, where the pulse is redistributed mainly to the ventricles and periventricular leg and bladder fibres. Therefore, in addition to the common alterations in aquaporin expression in AD and NPH, both disorders are characterised by perturbations in the distribution of intracranial pulsatility which otherwise drive the glymphatic system, and therefore, disruptions in the clearance of metabolites in proteins in the CNS.

Investigators have explored CSF shunting to treat AD, with the notion that CSF circulatory failure was implicated in both AD and NPH.[38] This may be related to the pathology of the glymphatic system. Silverberg *et al* noted mixed results; in a small cohort of patients, there was a reported benefit in mitigating cognitive decline for shunted patients with AD compared with non-shunted patients, but these benefits were not observed in larger cohorts for patients with AD with CSF shunting.[38] This is a line of inquiry that may warrant further investigation, particularly when analysing both conditions as disorders of intracranial pulsatility.

With vascular dementia and NPH, both conditions are characterised by arteriosclerosis with resulting impairments in CBF.[39] Otto Binswanger, when he first observed the eponymous form of vascular dementia, also noted 'enormously enlarged ventricles' in these patients.[39] While glymphatic impairment is less prominent in vascular dementia, this condition can be seen as a manifestation of more severe pathological progression of the arteriosclerosis also characterising NPH. Authors note that dementia patients with significant microvascular disease demonstrate elevations in cerebral microvascular pulsatility, which itself correlated with cognitive decline.[40] Therefore, vascular dementia, much like AD and NPH, may also involve windkessel impairment with resulting pulse redistribution, but more markedly to the cerebral microvasculature.

Given the overlap in clinical presentation and pathophysiology for these three conditions, we propose that these conditions exist on a spectrum based on the extent of each pathophysiological process, and each condition may ultimately manifest due to the predominance of one or more of these perturbations in physiology (figure 3). For AD, there is more severe disruption to glymphatic clearance concurrent with windkessel impairment causing redistribution of intracranial pulsatility to the ventricles and to some extent, the microvasculature. These processes may lead to accumulation of toxic proteins such as Aβ. With NPH, there is moderate arteriosclerosis leading to a preserved windkessel but redistribution of the pulsatility from the SAS to the ventricles and the periventricular leg and bladder fibres, as well as moderate CBF impairment and impaired glymphatic flow. However, there is minimal pulse redistribution to the capillaries. In vascular dementia, there is severe arteriosclerosis leading to a marked redistribution of pulsatility to the capillaries, leading to microvascular damage, reduced CBF and infarcts, and subsequent cognitive decline, while the perturbations to glymphatic clearance are less of a factor.

CONCLUSION

NPH represents a unique form of hydrocephalus manifesting as a disorder of the cerebral vasculature, characterised by arteriosclerosis and reduced intracranial elastance. There are multiple mechanisms underlying its pathophysiology, which include cerebral windkessel impairment causing redistribution of intracranial pulsatility from the SAS to the ventricles, reductions in CBF, impaired glymphatic clearance, reduced BBB integrity and alterations in venous hemodynamics. Furthermore, NPH shares similar pathological mechanisms to other neurodegenerative conditions such as AD and vascular dementia and can be viewed as existing on a spectrum with these conditions, with the predominance of one pathological mechanism leading to one condition vs the other. Further investigations are warranted to further assess these pathophysiological mechanisms, particularly the notion of NPH and other forms of hydrocephalus as a disorder of the distribution of intracranial pulsatility and perturbations to the cerebral windkessel.

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Contributors RM: original conceptualisation, literature review, writing, drafting and editing of manuscript. JB: writing, editing, literature review, figure design for manuscript. LY: experimental design for relevant theories in the manuscript. SF: editing of manuscript, figure design. PD: experimental design for relevant theories in the manuscript. ME: senior principal investigator/guarantor, editing manuscript.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

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