

Normal Pressure Hydrocephalus:

Diagnosis and Treatment Options

■ Abstract ■

Normal pressure hydrocephalus (NPH) is a relatively frequent but underdiagnosed geriatric disorder with symptoms of impaired gait and balance, overactive bladder, and cognitive decline in the presence of neuroimaging evidence of ventriculomegaly. Cerebrospinal fluid shunting is an effective treatment, although patients' response is variable, sometimes of short duration, and not always predictable. This might be due to poor patient selection or delayed surgery. Nevertheless, recent trials have indicated that shunt surgery is cost-effective and should therefore be recommended. Family physicians and general neurologists play a crucial role in ensuring a proper diagnosis and timely intervention.

Key words: normal pressure hydrocephalus, diagnosis, treatment

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Introduction

Hydrocephalus describes a clinical entity characterized by the excess accumulation of cerebrospinal fluid (CSF) within the brain, primarily in the ventricles. Hydrocephalus is separated into two categories: obstructive (or non-communicating) and communicating (or non-obstructive). Obstructive hydrocephalus

requires a physical blockage within the CSF flow pathway that results in upstream but not downstream increase of brain ventricles (Figure 1). In contrast, communicating hydrocephalus is caused by either an increase of CSF production (rare) or a defect in CSF reabsorption. Generally, obstruction proximal to the outlet foramina of the fourth ventricle

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Normal Pressure Hydrocephalus

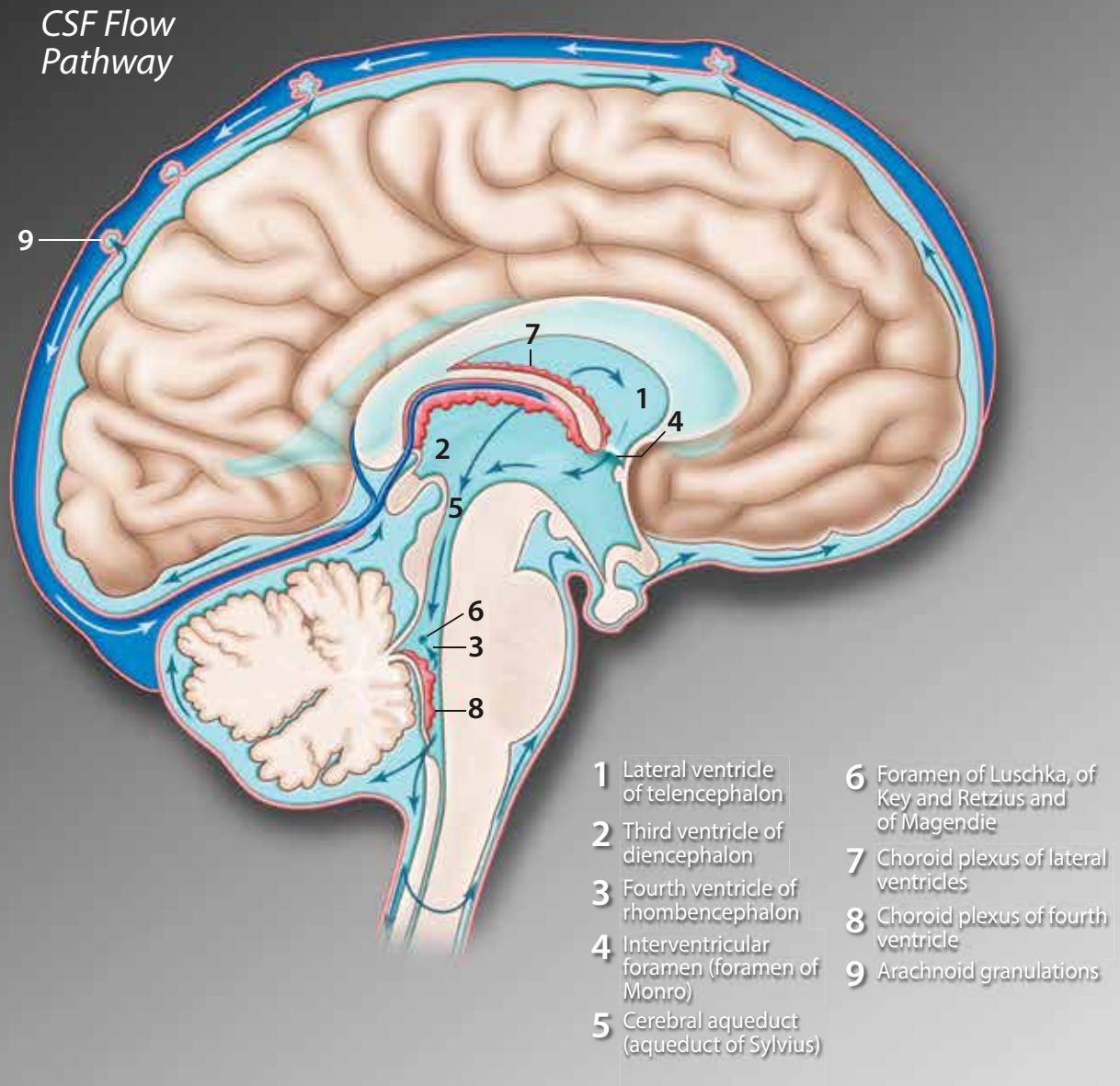


Figure 1.

The route of CSF is postulated to begin with production from the choroid plexus to flow through the ventricles, cisterns, and subarachnoid space ending, with reabsorption within the arachnoid granulations (macroscopic) and arachnoid villi (microscopic) on either side of the superior sagittal sinus. The choroid plexus produces 400-500 ml of CSF/24h and the total CSF volume is 120-150 ml. Thus, CSF recycles over three times per day. A new working hypothesis suggests that CSF is permanently produced and absorbed in the whole CSF system as a consequence of filtration and reabsorption of water volume through the capillary walls into the surrounding brain tissue.

causes an obstructive hydrocephalus while obstruction distal to the fourth ventricle causes a communicating hydrocephalus.

NPH IS ONE OF THE FEW REVERSIBLE CHRONIC NEUROLOGICAL CONDITIONS COMMON IN THE ELDERLY.

Normal pressure hydrocephalus (NPH) was first described by Hakim, Adams, et al. in 1965 as a clinical entity characterized by radiological evidence of communicating hydrocephalus (no obstruction, normal opening pressure, no signs/symptoms of increased intracranial pressure) and a classic triad of signs: gait disturbance, dementia, and urinary incontinence.¹

NPH has been recently subdivided into idiopathic (unknown etiology, see below) and secondary.² Secondary NPH occurs with a variable interval from meningitis, encephalitis, trauma (including concussion), subarachnoid hemorrhage, brain radiation, or any other condition potentially impairing CSF reabsorption; although secondary NPH patients tend to be younger and respond better to treatment than those diagnosed with idiopathic NPH, the current view is that secondary NPH should not be considered a separate entity.³ Most cases of NPH are idiopathic and are further differentiated depending upon the presence of disproportionate enlargement of the subarachnoid space (DESH, see below) (Figure 2).²



Key Point

NPH is common among elderly populations in Western countries, but it is largely underdiagnosed and undertreated.⁸

NPH is one of the few reversible chronic neurological conditions common in the elderly. The prevalence rate varies from 0.3% up to 3% in patients greater than 65 years old.⁴⁻⁶ According to the most recent prevalence study in the Western population and the recent Canadian census, over 79,000 Canadians are presently affected by NPH, a number that is predicted to double in 20 years.^{5,7}

Particularly when it is diagnosed early, neurosurgical shunting is an effective treatment for NPH. However, clinical presentation alone is usually not sufficient to diagnose NPH and recommend surgical treatment. Each of the NPH symptoms can have multiple potential etiologies, and enlarged ventricles can be seen in many neurodegenerative conditions characterized by brain atrophy. As a consequence of this complex scenario, although NPH is a common and treatable cause of dementia and mobility problems in the elderly population, it is largely underdiagnosed and undertreated.⁸

This review is intended for general physicians to highlight the pathophysiology and clinical features of NPH in order to increase awareness in the medical community and facilitate early recognition of NPH in patients and timely referral to specialized centres.

Pathophysiology

The pathophysiology of idiopathic NPH remains controversial and not well elucidated. Establishing the relationship between secondary forms is particularly difficult as many of the

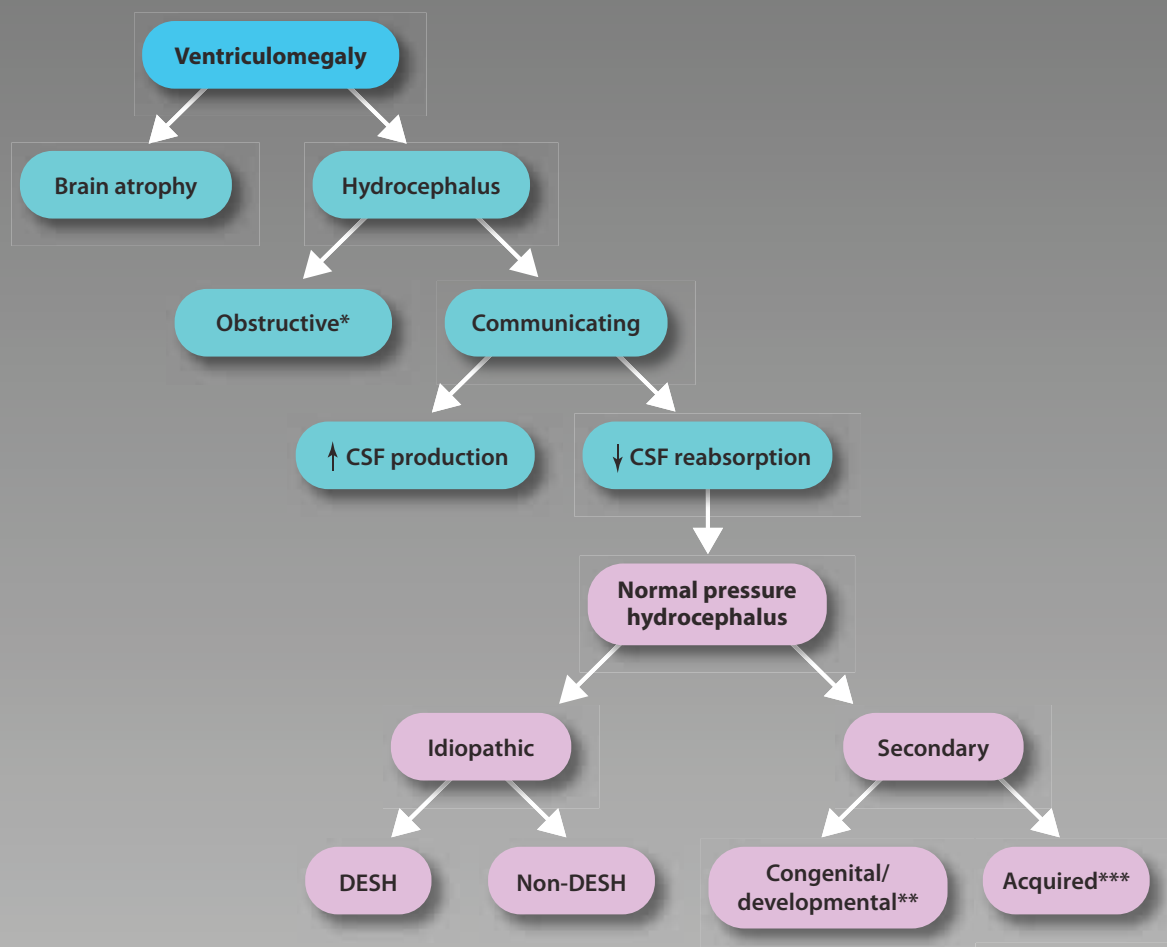


Figure 2.

A classification scheme of the different conditions characterized by ventriculomegaly. Some overlap among conditions is possible as indicated by asterisks. *: aqueductal stenosis can mimic the clinical picture of NPH (although the fourth ventricle should not be enlarged) and can co-occur in patients with NPH; **: enlarged head circumference is a risk factor for NPH that may indicate a congenital component to the disorder; in fact, a subset of 6-12-month-old infants with decreased uptake of CSF due to still immature arachnoidal granulations might present a "benign external hydrocephalus" that it is compensated by an enlargement of head circumference as their sutures are still open; ***: some acquired causes might not be diagnosed, thus overlapping with idiopathic cases.

established causes can occur many years before NPH symptoms manifest, and some might be congenital. Interestingly, a nation-wide Finnish cohort of 375 shunt-operated NPH patients found that 4.8% cases from 12 separate pedigrees had at least one shunt-operated relative whereas 42 cases (11%)

had relatives with two or more triad symptoms.⁹

Many pathophysiological theories have been suggested, the most prominent being disturbances in CSF dynamics and resistance resulting in brain parenchyma alterations and vascular abnormalities. According

to Hakim and Adam's hypothesis, NPH occurs when CSF absorption is decreased, resulting in increased intracranial pressure. Over time, ven-

resulting in parenchymal changes due to tissue compression and white matter ischemia. Accordingly, myelin basic protein—a marker of neuronal damage—has been shown to be elevated in NPH patients.¹⁷ On the other hand, some vascular risk factors (hypertension and diabetes) have been linked to an increased risk of NPH, thus pointing to the hypothesis that vascular white matter changes are coincidental or contributory rather than consequence of NPH.¹⁸ In addition, venous compliance in NPH is found to be reduced by up to 50%, particularly in the sagittal sinus.¹⁹ Overall, this process can result in reduced cellular metabolism and clearance of toxins, specifically amyloid B protein and microtubular associated protein, possibly favoring AD-like neurodegenerating.²⁰

THE NPH TRIAD OF GAIT, COGNITIVE, AND URINARY DYSFUNCTION DEVELOPS INSIDIOUSLY.

tricular enlargement occurs as a compensatory mechanism. This results in a new intracranial pressure steady state.¹ How the increased pressure and ventricle enlargement produce a frontal lobe dysfunction (able to explain most of the NPH symptoms) is another unsolved issue, particularly because any plausible theory should explain two contrasting phenomena: the relatively complete reversibility of symptoms with CSF shunting and the coexistence of vascular and neurodegenerative features. In fact, autopsies of NPH patients frequently report the pathological hallmarks of vascular diseases or Alzheimer disease (AD).^{10,11} On the other hand, multiple studies have reported a decreased glucose metabolism or cerebral perfusion of several areas (periventricular white matter, temporal lobe, frontal lobe, thalamus, and basal ganglia) which are variably reverted by CSF tap testing or shunting.¹²⁻¹⁵

It is hypothesized that NPH-related ventricle enlargement displaces fibers connecting cortical and subcortical regions, particularly within the frontal lobe.¹⁶ Furthermore, CSF flow is pushed through the Virchow-Robin spaces into brain parenchyma, thus

Diagnosis

In 2012, the second edition of the international Japanese guidelines for normal pressure hydrocephalus was published, outlining the most up to date diagnostic criteria.² A mixture of clinical, neuropsychological, and diagnostic imaging is key to establishing diagnosis.

Clinical Manifestations

The NPH triad of gait, cognitive, and urinary dysfunction develops insidiously. A common but false belief is that all symptoms should be present in order to make a diagnosis and refer the patient to a neurologist. In fact, it is estimated that only 60% of patients present with the classic triad; some symptoms (especially the urinary ones)



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might not develop at all. On the other hand, other symptoms (dementia) might not respond to surgery, especially when it is performed too late.

Gait

NPH usually begins with symmetrical gait problems, which are typical of higher level gait disorders and lower body parkinsonism.²¹ NPH gait is characterized by a broad base (to correct for a multidirectional instability), outward feet deviation, small shuffling steps, and difficulty initiating movements, particularly during turning; some patients may also display freezing of gait, which is common in parkinsonisms and is defined as the inability to initiate or continue steps. Interestingly, NPH patients should not manifest signs of upper-body parkinsonism and therefore their arm swinging during

walking might be normal or exaggerated.²¹ Gait and balance can be clinically evaluated with dedicated scales (e.g. the gait scale developed by the Dutch normal pressure hydrocephalus study), standard tools such as the Timed Up and Go Test, the Berg Balance Scale, the Functional Reach Test, or with gait analysis (Figure 3).

Cognition

Frontal lobe executive dysfunction and psychomotor slowing progressively leading to dementia is another common finding in NPH patients. Useful screening tools are the Mini-Mental Status examination²² or the Montreal Cognitive Assessment,²³ the latter being more sensitive as it is tailored for executive function assessment. Other tests can be used, including the recently developed counting-backward test.²⁴ More extensive neuropsychological testing

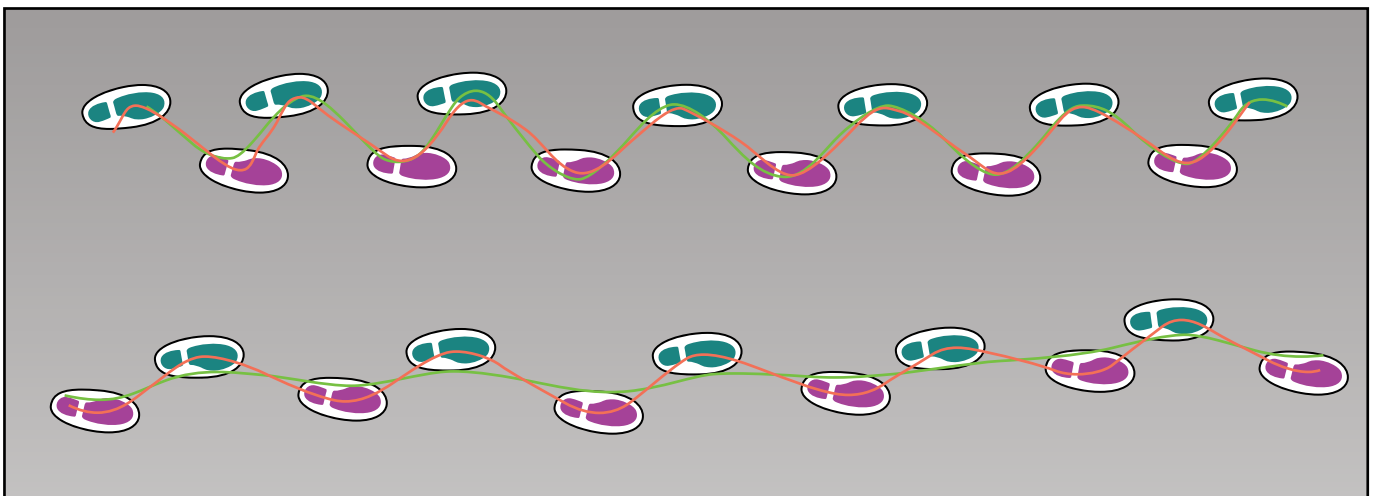


Figure 3: TWH's Adult Hydrocephalus Clinic Experience

Gait analysis of a NPH patient before (top) and after (bottom) tap test: 2h after the removal of 40 cc of CSF the patient is faster and steadier as shown by the more regular stepping and narrower base of support.

might be used when the differential diagnosis with other dementias is difficult, or to monitor the effect of surgical treatment. In fact, NPH is associated more with executive frontal lobe and attention deficits than with memory impairment,

“ASYMPTOMATIC VENTRICULOMEGALY WITH FEATURES OF IDIOPATHIC NPH ON MRI” IS AN IMPORTANT RADIOLOGICAL FINDING IN PATIENTS WITHOUT CLINICAL SIGNS OF NPH.

apraxia, or language impairment, as seen in AD.^{25,26}

Urinary symptoms

Urinary dysfunction results from detrusor muscle over activity, thus leading the variable combination of urgency, frequency, nocturia, and urge incontinence.²⁷

Other symptoms

Other rare and inconsistently reported symptoms include apathy, anxiety, and daytime sleepiness.²⁸ In some cases, parkinsonian signs also responsive to L-dopa have been reported and two theories are currently in place to explain this combination: a reversible parkinsonism caused by the effects of NPH on nigro-striatal pathways²⁹ or the coincidental occurrence of the two diseases in the same individual.³⁰

Imaging

Any patient with at least one symptom of the aforementioned triad should undergo brain magnetic resonance imaging (MRI) or computed tomography (CT) if MRI is contraindicated. Figure 4 shows the principal neuroimaging features seen in NPH. Ventricular enlargement without signs of CSF obstruction should raise a suspicion of NPH. As ventricular enlargement occurs with other dementias, and to some extent also with normal aging, a ratio of maximum width of the frontal horns of the lateral ventricles and the maximal internal diameter of the skull, known as the Evans index, has been proposed. All physicians should know that an Evans index >0.3 points to NPH. There has been recent debate over its accuracy and reliability in NPH diagnosis and some researchers have proposed a cutoff value of 0.33. A recent population-based sample on 1235 subjects over 70 years concluded that the Evans index ranged from 0.11 to 0.46, mean value in the total sample was 0.28 ± 0.04 , but 255 subjects (20.6%) had values >0.3 ; individuals with dementia had a mean value Evans index of 0.31 ± 0.05 , and those with radiological signs of NPH had a mean value of 0.36 ± 0.04 .³¹

“Asymptomatic ventriculomegaly with features of idiopathic NPH on MRI” is an important radiological finding in patients without clinical signs of NPH. These patients do not have NPH but should be monitored for the potential development of future gait disturbance.³²

All physicians should be also familiar with DESH, particularly



Key Point

Gait and balance impairment are early signs of NPH and not all 3 of the triad symptoms should be present in order raise a suspicion of NPH and refer the patient to a neurologist.

because the latter might mimic brain atrophy (Figure 4). In fact, a lateral enlargement within the temporal and frontal horns can be present in NPH and some studies have suggested that DESH is a specific marker for NPH.³³ Over the years many other radiological signs have been proposed, such as aqueductal flow void caused by the increased CSF flow velocity³⁴ or specific tractographic findings.³⁵

Particularly with the conventional proton density-weighted spin-echo images of the past, CSF flow void can be seen in other ventricles and it is indicative of hyperdynamic CSF (similar to the flow voids seen in arteries on MRI). This observation led to the development of more sophisticated phase-contrast MRI techniques to evaluate CSF flow.

Temporary CSF drainage

Once neuroimaging has ruled out an obstructive hydrocephalus, a large volume lumbar puncture (tap test) can be performed by removing 30-50 ml of CSF and evaluating the effects on gait 1.5-2h after the test; more controversial is the effect on cognition.³⁶ Although it is standard practice for patients to lie flat for 10-30 minutes after the lumbar puncture, some experts believe the sensitivity of the test is increased by having the patient remain upright and engage in modest activity (if tolerated). Although the safety of this approach has not been rigorously evaluated, headache and nausea after lumbar puncture are uncommon in the elderly NPH population.

A positive tap test is generally a positive predictor of shunting, although its sensitivity and specificity are not optimal. A number of non-responders can still benefit from surgery, while in some subjects the improvement merely reflects a placebo response. This test also offers the opportunity to measure the opening pressure (that should be within 5-18 mmHg or 70-245 mmH₂O) and collect CSF for routine tests; although research on CSF biomarkers for dementia is rapidly expanding, it has no clinical role in NPH.^{17,37,38}

In case of a negative response, the tap test can be repeated removing a greater amount of CSF. Alternatively, an external lumbar drainage for 72 hours can be performed. This is a more accurate

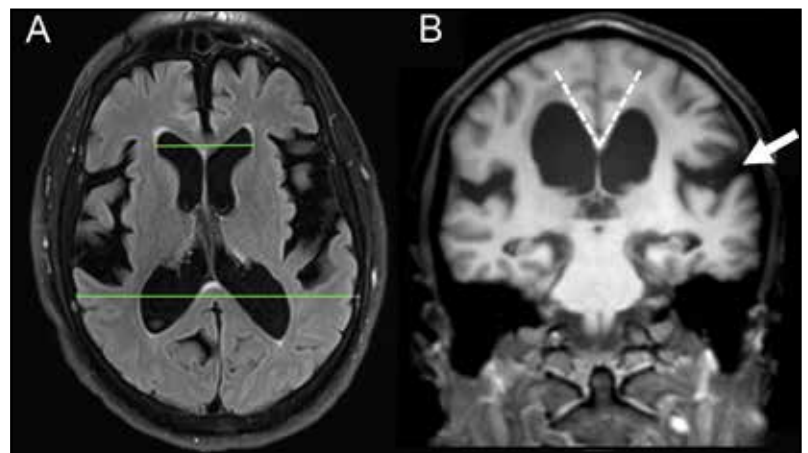


Figure 4: The typical MRI finding of a NPH patient.³⁶ A) Axial FLAIR sequences show an Evans index >0.3 (this is the ratio between the maximal frontal horn ventricular width divided by the transverse inner diameter of the skull at the same level, in this case: $4.52/12.62 \text{ cm} = 0.36$); B, Coronal T1-weighted sequence shows narrow sulci at high convexity, acute callosal angle (dotted line) and dilated bilateral sylvian fissures (arrow), in keeping with a “disproportionately enlarged subarachnoid space hydrocephalus” (DESH) subtype, a condition mistakenly diagnosed as temporal lobe atrophy if only assessed with axial slices (see A).

and better predictor for surgical outcome, but it limited by its invasiveness and need for hospital admission.³⁹

Differential diagnosis and comorbidities

There is a degree of overlap between clinical symptoms of NPH and other neurodegenerative conditions, making it difficult to clinically differentiate. In addition, NPH typically affects patients over the age of 60 (70 years old on average), thus meaning that a number of comorbidities—including other neurological disorders—can be present (see pathophysiology). Comorbidities such as diabetes and cardiovascular disease are in turn linked to poorer performance in NPH patients.⁴⁰

More recently it has been postulated that previously reported cases of “dual” pathology (e.g., NPH and Parkinsonism) actually represent the “hydrocephalic presentation” of selected neurodegenerative disorders.⁴¹

From a practical standpoint the screening process should include: a complete blood count, biochemical profile, vitamin B12, folate, thyroid-stimulating hormone, rapid plasma reagin, Lyme serology, and vitamin D.³⁶ Spine MRI (particularly to rule out spinal stenosis), electromyography, nerve conduction velocity, and urology consultation should be arranged if clinically indicated. Significantly, it has been recently proposed that a normal sense of smell might be useful in differentiating NPH from other neurodegenerative

disorders, particularly AD and parkinsonisms.⁴²

Treatment

No medical treatment is effective in NPH; the first step in treating the NPH patient is treating all of the potential comorbidities, discontinuing drugs with a negative impact on cognition and mobility (benzodiazepines, neuroleptics, etc.), and—although not always needed—trying L-dopa to rule out co-existing parkinsonism. Referral to a neurosurgeon is usually made by the neurologist after the diagnosis is confirmed and comorbidities are treated.³⁶

Ventriculo-peritoneal shunting (VPS) is the mainstream treatment for NPH with success rates ranging from 50% to 80%.^{43,44} Complications, such as subdural hematoma, shunt infection, and shunt obstruction can occur and typically require neurosurgical intervention. Gait improves the most from VPS, although studies have also shown improvement in cognitive functioning post shunt.⁴⁵⁻⁴⁸ A significant improvement in urinary symptoms, specifically urinary urgency and urge incontinence, as well as overall quality of life (particularly in women and younger patients), has been also reported.⁴⁹

These data were confirmed by the SINPHONI (Study of Idiopathic Normal Pressure on Neurological Improvement) study, which was a multicentre prospective cohort study in which 100 NPH patients were enrolled to test the safety and efficacy of VPS.⁵⁰

The variability of surgical outcome is the function of a number



Key Point

Any patient with at least one symptom of the NPH triad should undergo a brain MRI or computed tomography CT (if MRI is contraindicated).

of factors: diagnostic difficulties, patient's age (younger is optimal), occurrence of severe cognitive involvement, postural instability, other comorbidities, and disease duration (better results with shorter duration).³⁶ Clinically, patients presenting with early or severe dementia have worsened outcome, while those with primary gait disturbance have better results.^{51,52} Certain MRI characteristics, CSF flow dynamics, and results

of temporary drainages can indicate a positive response to shunting.

In VPS, a shunt is inserted with a proximal catheter into a ventricular space and a distal end in the peritoneal cavity (Figure 5). In between there might be two types of valve: gravitational and programmable. Gravitational valves open in response to the amount of fluid present. Programmable valves require a set pressure point to open and,

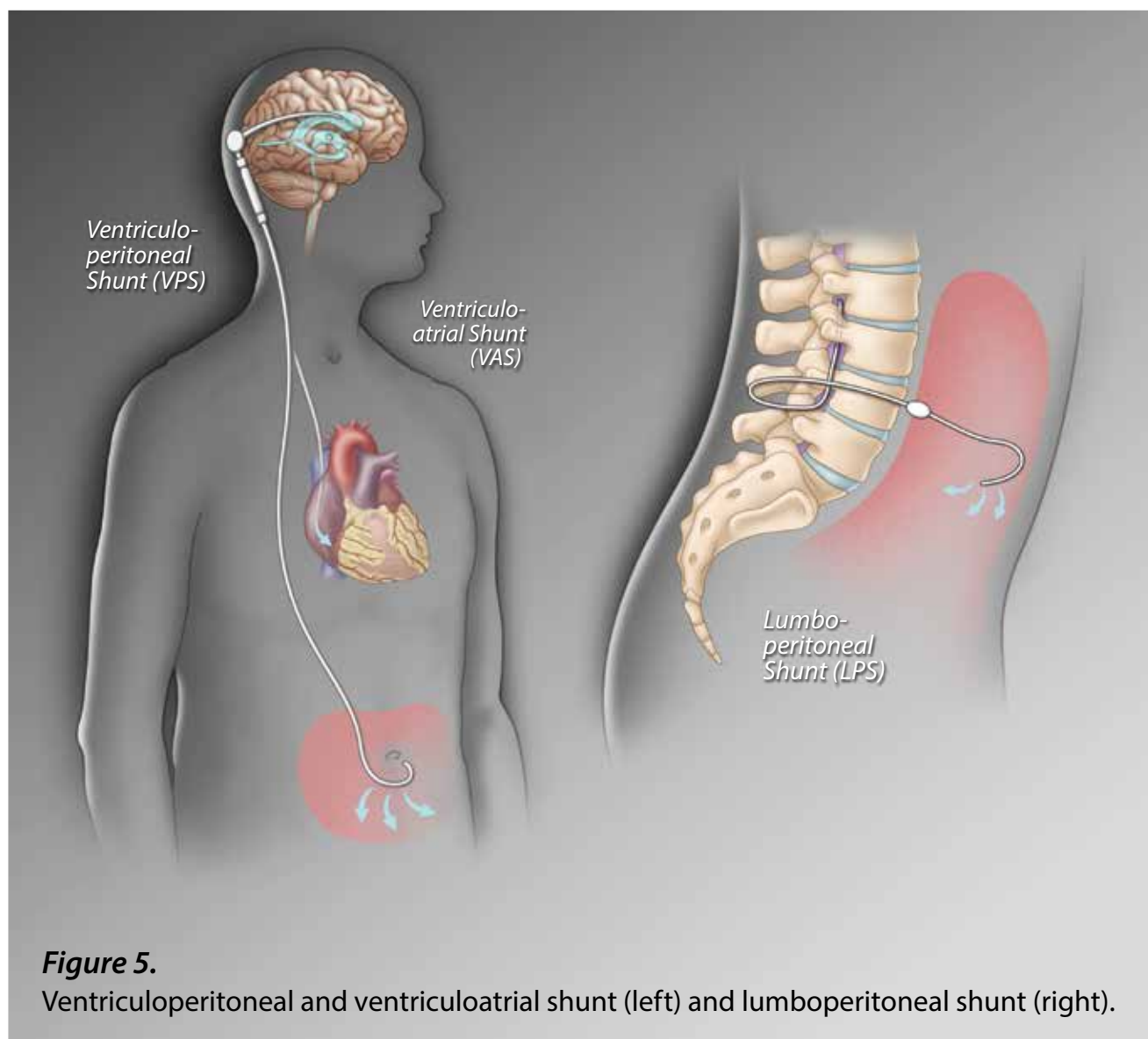


Figure 5.

Ventriculoperitoneal and ventriculoatrial shunt (left) and lumboperitoneal shunt (right).



Key Points

Family physicians have a crucial role in ensuring a proper diagnosis and timely intervention. In this respect, a few rules should be remembered:

1. NPH is common among elderly populations in Western countries, but it is largely underdiagnosed and undertreated.⁸
2. NPH is one of the few reversible chronic neurological conditions in the elderly because neurosurgical shunting is an effective treatment, especially if performed early.³⁶
3. Gait and balance impairment are early signs of NPH and not all 3 of the triad symptoms should be present in order raise a suspicion of NPH and refer the patient to a neurologist.³⁶
4. Any patient with at least one symptom of the NPH triad should undergo a brain MRI or computed tomography CT (if MRI is contraindicated).³⁶
5. Important MRI/CT findings are an Evans index >0.3 and DESH, which should be investigated because it might mimic brain atrophy.³³

if not correctly adjusted, possible over drainage or underdrainage can occur, leading to subdural hematomas or ineffective shunting.

The SVASONA (Shunt Valves plus shunt Assistant versus Shunt valves alone for controlling Overdrainage in idiopathic Normal pressure hydrocephalus in Adults) trial compared the efficacy of gravitational versus programmable valves. Findings suggested that gravitational valves might be a better option for NPH patients due to reduction in over drainage of CSF.⁵³ On the other hand, the International and Japanese guidelines find that adjustable shunt valves offer the advantage of being able to gradually lower the pressure setting until symptom improvement is achieved and to raise the pressure setting if low-pressure symptoms or complications emerge.^{2,54} Adjustable valves can be used to safely manage NPH patients who need chronic anticoagulation.⁵⁵

Adjustable valves have been used in an elegant, single-centre, prospective, double-blind trial randomizing NPH patients to receive low opening pressure (active shunting) or high opening pressure shunt (sham shunting).⁵⁶ Although the study had to end prematurely due to difficulties in enrolling patients, it showed the statistically significant advantage of active shunting in improving walking speed when compared to sham shunting: 43% vs. 0% at the study endpoint of 3 months ($p=0.02$).⁵⁶

Ventriculoatrial shunting (VAS) can be used to manage NPH but it is less frequently used due to concerns associated with cardiopulmonary and renal complications. A recent retrospective chart review found that VAS patients were less likely to experience shunt obstruction and require shunt revision compared to VPS patients.⁵⁷

An alternative to VPS and VAS is lumboperitoneal shunting (LPS),



Key Point

Important MRI/CT findings are an Evans index >0.3 and DESH, which should be investigated because it might mimic brain atrophy.

whereby the proximal catheter is inserted into the lumbar subarachnoid space. Although it avoids an invasive intracranial procedure associated with the risk of subdural hematoma,⁵⁸ LPS has been underutilized by neurosurgeons due to a relatively high prevalence of malfunctions, shunt blockage, radiculopathy, and infection.⁵⁹ Nevertheless, the recent SINPHONI-2 trial confirmed the efficacy of LPS with an open-label, two-arm, delayed start design (surgery was postponed 3 months in one study arm).⁶⁰ The most common adverse effect was postural headache and the most serious was cerebral infarct (7% of patients); shunt malfunction or placement issues were also reported but were easily corrected.⁶⁰

Finally, although endoscopic third ventriculostomy is typically used for obstructive hydrocephalus, it might offer a device-less alternative treatment for NPH.⁶¹ The reason for its efficacy is not clear: it might facilitate CSF circulation so that the excessive CSF can be absorbed more effectively, or it might treat a subclinical underlying aqueductal stenosis mimicking the clinical picture of NPH.

Conclusions and take-home messages

NPH is a disorder prevalent in the elderly with symptoms of impaired gait and balance, overactive bladder, and cognitive decline, as evidenced by neuroimaging of ventriculomegaly. In spite of attempts to predict the clinical outcome, response to shunting is variable, sometimes of short duration, and not always pre-



Clinical Pearls

A suspicion of NPH should be raised for those patients with gradually progressive gait disorders characterized by instability (broad base) and shuffling steps; no other parkinsonian signs should be noticed, particularly in the upper body. Urinary dysfunction might be absent and cognitive problems are typically less severe than the motor problem (particularly at onset). In a patient with a clinical suspicion of NPH, brain MRI should be ordered and a referral to a neurologist should be made.

The neurologist will exclude other neurodegenerative conditions and other clinically relevant diseases affecting gait (e.g. neuropathy, spinal stenosis). Afterwards a tap test will be arranged, bearing in mind that the sensitivity of the test is far from ideal and that patients are prone to placebo response. When the suspicion of NPH remains high (also in case of negative tap test) a referral to neurosurgeon is made by the neurologist. In less clear-cut cases, another tap test or prolonged lumbar drainage can be done. Some other cases are only clinically followed-up, however taking into account that a delayed intervention might not provide the benefit of early surgery.

dictable.⁶² This might be due to poor patient selection or delayed surgery. In fact, the accuracy of current diagnostic tests is far from optimal, particularly when differentiating NPH from other neurodegenerative conditions. Clinical presentation alone is usually not sufficient to diagnose NPH and recommend surgical treatment. Each of the NPH symptoms can have multiple potential etiologies, and enlarged ventricles can be seen in many neurodegenerative conditions characterized by brain atrophy. In addition, it is recognized that patients with long-standing NPH characterized by cognitive and balance impairment are less likely to

gain functionality after shunting. Of note, the recent combined cost-effectiveness analysis of SINPHONI and SINPHONI-2 trials concluded that the total cost for NPH patients shows a positive return on investment in as soon as 18 months (VPS) and 21 months (LPS), indicating that shunt surgery is a cost-effective treatment and therefore recommended.⁶³

The limitations of the current knowledge and model of care in NPH as well as the future directions of the scientific and medical community have been recently summarized at the third National Institutes of Health-sponsored symposium “Opportunities for Hydrocephalus Research: Pathways to Better Outcomes.”⁶⁴

Conflicts of Interest

Dr. Fasano is supported by grants from University of Toronto, Michael J. Fox Foundation; he received speaker and/or consulting honoraria from UCB pharma, Medtronic, Boston Scientific, Abbvie; he served on the scientific advisory board for Abbvie, Boston Scientific and TEVA.

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