Three decades of normal pressure hydrocephalus: are we wiser now?

Some adults with the clinical triad of gait disturbances, mental deterioration, and urinary incontinence associated with chronic hydrodynamic hydrocephalus will improve after a CSF diversion procedure, even when the CSF pressure is normal at lumbar puncture. This intriguing paradox was designated normal pressure hydrocephalus (NPH) by Hakim et al, and has continued to excite both clinicians and researchers seeking pathophysiological mechanisms in CSF hydrodynamics and both the clinical predictors and appropriate tests that would facilitate the accurate selection of candidates for a shunt.

Experiments in chronic hydrocephalic animals and hydrodynamic studies in humans have shown that impairment of CSF flow and episodes of slightly raised CSF pressure are the basic defects in NPH. Our understanding of persistent or even increasing ventricular enlargement and clinical deterioration despite a "normal" CSF pressure is still incomplete, however. Periods of increased intraventricular pressure, including short lasting B waves, persistence of a slight pressure gradient between the ventricles and the cerebral convexity, a "waterhammer effect" due to increased CSF pulse pressure waves on the ventricular walls, and altered viscoelastic properties of the ventricular wall have been described as possible contributory mechanisms. It is still unclear whether there is a cause and effect relation between these phenomena and NPH or not.

The site of impaired CSF flow may be situated within the ventricles or in the subarachnoid space. In non-communicating NPH, partial obstruction to CSF flow within the ventricular system is mainly due to non-tumoural aqueduct stenosis. In communicating NPH, impairment of CSF flow is distal to the 4th ventricle, most often at the level of the basal cisterns ("cisternal block"). About 50% of communicating hydrocephalus is idiopathic, the other 50% secondary to subarachnoid haemorrhage, meningitis, cranial trauma, or intracranial surgery. There are neither physiological nor pathological arguments to maintain the myth that NPH may be due to defective CSF absorption through the arachnoid villi. This would not lead to ventricular enlargement, as there is no pressure gradient between the ventricles and the convexity.

Clinical deterioration is probably due to diminished periventricular blood flow, possibly caused by hydrocephalic compression and stretching of the periventricular arterioles and venules, as shown in experimental hydrocephalus and in studies on cerebral blood flow in NPH. This would lead to a state of "misery perfusion"; with periventricular blood flow reduced sufficiently to result in axonal dysfunction but not enough to cause irreversible loss of cellular integrity. Narrowed periventricular arterioles due to hyaline vessel wall degeneration in hypertensive patients might be another precipitating factor and would explain why the prevalence of vascular risk factors in NPH is increased. Prolonged periventricular ischaemia would eventually result in myelin disintegration and irreversible axonal loss, possibly explaining why some patients with NPH do not improve after a shunt.

Precise epidemiological data on NPH are lacking. Katzman suggested that the total number of cases in the United States is 10,000 ± 5000, about one per neurologist. In published series, NPH accounts for 0 to 6% of cases of dementia, the variability of these percentages being partly explained by the use of different diagnostic criteria and referral biases. In a recent study, the incidence of clinical improvement after a shunt in 166 patients with presumed NPH was only 2.2 per million persons per year. Assuming that the incidence of dementia in the same area might be estimated at 600 per million persons per year, shunt responsive NPH would represent only about 0.4% of the causes of dementia.

Initially, NPH was thought to be a disease occurring mainly in the presenium but later many series contained many patients in the sixth decade or older. A review of the literature including 21 articles and more than 1000 patients shunted for presumed NPH showed that substantial improvement occurred in about 30% of idiopathic NPH, in 50–70% where the aetiology was known. The total number with postsurgical complications was 30–40%, resulting in death or severe residual morbidity in 5–15%.

Signs and symptoms

Gait difficulties are the first, in some cases the only, apparent clinical sign, and these are the most likely to improve after shunting. There may be difficulty in initiating walking (“magnetic phenomenon”), postural instability and, in more advanced stages, a short-stepped shuffling gait. Hyper-reflexia—mainly in the lower extremities—and extensor plantar response may be present. These features are not specific, as they may also be seen in other cerebral diseases such as subcortical arteriosclerotic encephalopathy. The often used term of “gait apraxia” is controversial and inappropriate in NPH. This is illustrated by the fact that patients with NPH may
execute nearly intact walking movements when minimally supported or when lying down.

The cause of gait impairment in hydrocephalic patients is probably multifactorial, including stretching or destruction of the paraventricular corticospinal fibres,43 disconnection of basal ganglia from the frontal cortex, and uninhibited antigravity reflexes and cocontraction of agonists and antagonists during walking.44

"Dementia" is an unfortunate term with which to designate the mental impairment in NPH, because most patients with shunt responsive NPH have only a slight or moderate mental deficit,16,16 which would not fit the criteria of dementia as defined in the Diagnostic and statistical manual of mental disorders-revised (DSM-III-R).15 The mental deficit is of the "subcortical" type, resembling that seen in frontal disorders: forgetfulness, inertia, inattention, decreased speed of complex information processing, and impaired ability to manipulate acquired knowledge being the most prominent features.56-60 When intellectual loss is predominant in the clinical picture, another cause of dementia should be considered.

The view that the clinical distinction between Alzheimer's disease and NPH is difficult is now hardly tenable, especially in the early stages of these diseases. In NPH there is not only absence of cortical dysfunction, but the pattern of memory deficit is also different: memory functions depending on the functional integrity of the frontal lobes are impaired, resulting in a discrepancy between severely impaired delayed recall and relatively mildly affected or even normal delayed recognition,49 as indeed are seen in other diseases with mental deterioration of the subcortical type.50-51 This contrasts with Alzheimer's disease, in which encoding deficits and impaired recognition are more prominent.50-51 Consequently, the assumption that hydrocephalic amnesia is attributable to enlarged temporal horns and hippocampal dysfunction51 is improbable, given the type of memory impairment. When dementia predominates in the clinical picture, concomitant Alzheimer's disease should be suspected and may be confirmed by hippocampal atrophy on CT5' or MRI.14

Urinary incontinence is a late sign. An increased urgency, however, is almost always present but often only mentioned when specific inquiries are made.56 Urinary incontinence is due to damaged periventricular pathways to the sacral bladder centre,17,55 with subsequent decreased inhibition of bladder contractions. This has been shown by urodynamic investigations, indicating hyper-reflexia and instability of the bladder detrusor muscle, without evidence of concomitant defective sphincter control.17,55

A frequent misconception is that the cause of urinary incontinence is due to a so called "incontinence sans gêne". This is only the case in the most severe forms, when bladder hyper-reflexia is associated with lack of concern for micturition, due to severe frontal lobe dysfunction.

**Diagnostic tests**

**NEUROPSYCHOLOGICAL ASSESSMENT**

The use of brief mental screening tests such as the mini-mental state examination (MMSE)56 may prove inadequate because these are not able to detect slight cognitive impairment,57 which is often seen in the mental deficit of the "subcortical" type. Studies that have used the MMSE criteria of dementia for diagnosing NPH49 are flawed by a diagnostic bias, as they excluded all patients with NPH who had mild mental impairment—the very patients with the best surgical prognosis. Even in the early stages of the syndrome, psychometric tests will reveal intellectual decline, provided that the test battery includes tasks that can detect frontal lobe dysfunction, such as the trail making test and the Stroop test. Another advantage of frontal tests is that they are very sensitive in detecting a subtle cognitive decline—for example, in cases where shunt dysfunction is suspected.16 Although the test profile may not differentiate NPH from other subcortical dementias, the absence of cortical dysfunction and the "frontal" pattern of mental deficit in NPH would render the diagnosis of Alzheimer's disease improbable.

**NEUROIMAGING TECHNIQUES**

Computed tomography has greatly improved the identification of NPH. In "classic" cases, CT usually shows ventricular enlargement out of proportion to cerebral atrophy, including rounded frontal horns and enlarged temporal horns without hippocampal atrophy.60-62 Unfortunately, atypical features such as mild or moderate cortical atrophy or periventricular abnormalities of white matter suggestive of ischaemic lesions do not preclude clinical improvement after a shunt.60-62 Frontal and occipital periventricular lucencies consistent with transendymal CSF absorption are not often seen in NPH.64

Potentially misleading is that in both subcortical arteriosclerotic encephalopathy and NPH periventricular lucencies may be selectively located around the frontal horns and that frontal periventricular lucencies due to frontal periventricular ischaemia may be misinterpreted as due to transendymal CSF absorption.17

Jack et al64 pointed out that the high sensitivity of MRI in detecting ischaemic white matter lesions may lead to problems in deciding whether these lesions explain the clinical picture or are merely asymptomatic findings in patients who really have NPH. A patient with NPH and an incorrect MRI diagnosis of subcortical arteriosclerotic encephalopathy may have been denied the potential benefit of a shunt. In patients with substantial and global cognitive impairment, MRI may facilitate differentiating Alzheimer's disease from NPH by measuring the mean cross sectional volume of the hippocampal body, which is atrophic in Alzheimer's disease but not in NPH.54

T2 weighted images may show a "CSF flow voiding sign"55 consisting of a decreased MR signal, mainly in the aqueduct, which correlates with the velocity of pulsatile CSF flow. In shunt responsive communicating NPH, the aqueductal CSF flow velocity may be increased,66 but the relevance of this finding is still unclear, as there is no high correlation between a pronounced CSF flow voiding sign and NPH,67-68 and successful shunts will not necessarily result in a decrease of the CSF flow voiding sign.66 Many other MR findings pertaining to NPH reported in small series have not as yet been independently verified.

**REMOVAL OF CSF**

Lumbar puncture with removal of 40–50 ml CSF may be followed by a transient or, in rare cases, prolonged clinical improvement.16 Wikkelso et al assumed that the degree of postsurgical improvement could be predicted by the degree of improvement after a CSF tap.70 Although these results have not been reproduced by others, the CSF tap test is now used worldwide, probably because it is easy, rapid, and cheap. There is increasing evidence, however, that the predictive accuracy of a CSF tap is limited, particularly because of the high rate of false negative results.17 Haan and Thomee71 and Hanley et al71 suggest that, even in the case of a "negative" CSF tap test, the effect of continuous external lumbar drainage of about 150–200 ml daily for three to five days
may accurately predict the outcome after a shunt. This test is technically simple and applicable in most neurological and neurosurgical departments, as disposable equipment is now available. Complications associated with the test, such as radicular inflammation or meningitis, however, may occur. As the reported series was small and a meaningful postsurgical benefit may be delayed by several weeks or even months, these promising results should be confirmed by a larger multicentre prospective study with long term follow up.

CISTERNOGRAPHY
Isotope cisternography to assess CSF circulation was first used by Bannister et al in NPH. With the advent of CT, CT cisternography was also used to show disturbed CSF circulation as "reversed CSF flow". Despite the experiences of many investigators that cisternography is an unreliable predictive test and the recent finding that the test did not add to the diagnostic accuracy of combined clinical and CT criteria, cisternography remains one of the most popular tests. This may be due to the reluctance of clinicians to change their practice, despite the evidence that a particular procedure is unreliable.

MEASUREMENTS OF CEREBRAL BLOOD FLOW AND METABOLISM
It has been suggested that cerebral blood flow studies are of value in predicting the outcome after shunting. Recent cerebral blood flow studies with single photon emission computed tomography (SPECT) transcranial Doppler sonography of the middle cerebral artery, and measurements of cerebral metabolism with PET have shown decreased cerebral blood flow and metabolism in NPH, most pronounced in the frontal and the periventricular areas. In some patients with shunt responsive NPH, the cerebral blood flow increased after CSF removal or after a shunt. Many inconsistencies remain: the areas of impaired cerebral blood flow differ from study to study, ranging from widespread cerebral hypoperfusion to selective ischaemia in the frontal periventricular areas; there is no good correlation between changes in cerebral blood flow and outcome after CSF diversion; at long term follow up recurrence of decreased cerebral blood flow may occur without concomitant clinical deterioration. It is probable that one of the reasons for the variable results is that, in some studies, techniques for measuring cerebral blood flow in patients with NPH were not sensitive enough to detect subtle changes in the frontal periventricular areas.

PRESSURE MONITORING AND HYDRODYNAMIC TESTS
Continuous intracranial pressure monitoring may show CSF pressure oscillations with a frequency of 0.5–2 per minute (B waves). The aetiology and pathological role of B waves are still unclear as they are a physiological phenomenon occurring in healthy persons. Investigations in centres with CSF hydrodynamic expertise have shown that the occurrence of B waves is much increased in shunt responsive NPH, sometimes exceeding 50% of the observation time. Unfortunately, the results of continuous intracranial pressure monitoring in less specialised neurosurgical centres are not known, and there is evidence that in many of them, it is not in routine use, mainly due to technical problems or questionable results.

There are still doubts about the reliability of lumbar CSF infusion tests, which measure the resistance of CSF outflow (Rout) by lumbar or ventricular infusion of artificial CSF. Variable results have been obtained. Some investigators found the test reliable with a high rate of postsurgical improvement when the Rout was higher than 15–20 mm Hg/mL/min. Others have deceptive experiences with this test. The same holds true for the CSF conductance test (Cout, the reciprocal of Rout), consisting of measuring CSF reabsorption by constant lumboventricular or ventriculoventricular CSF infusions at different CSF pressures. The test was highly reliable in the hands of some investigators, but less predictive in other series. In view of its invasiveness and the need for technical expertise, Cout is not suitable for widespread clinical use.

Unfortunately, the common feature of most studies on the accuracy of ancillary tests for predicting the outcome after shunting is the lack of assessment of the pretest probability of shunt responsiveness based on a global scale combining well established clinical criteria with CT and MR data. Hence, we do not know which of the reported ancillary tests has the best additional predictive value, and, particularly in the cases of invasive tests, whether the increase in predictive accuracy would be high enough to justify its use in all patients in whom diagnostic doubts remain.

Conclusion
Are we now wiser after three decades of shunting patients with NPH? In some ways we are. Thanks to 30 years of clinical studies and the availability of new neuroimaging techniques, we are able to identify patients with either probable or improbable shunt responsive NPH with a fairly high rate of diagnostic accuracy. There is now a consensus that, when there is a short history, a known cause of hydrocephalus, predominance of gait disorders, and CT or MRI suggesting hydrodynamic hydrocephalus, about 50–70% or more will do well after surgery. It is also justified to shunt patients with an unequivocally positive CSF tap test. Shunt response is improbable in patients who are predominantly demented, or who have evidence of substantial cortical atrophy, extensive white matter involvement, or both. Most neurosurgeons will not submit these patients to the risks of a shunting procedure because the chance of a postoperative disaster is higher than that of an unexpected surgical success.

Differential diagnostic problems may still arise in some patients with subcortical arteriosclerotic encephalopathy, whose clinical picture may be similar to that of NPH. The term "Hakim’s clinical triad" is misleading because it may suggest that, in patients with this triad, NPH ranks at the top of the differential diagnostic list. In fact, subcortical arteriosclerotic encephalopathy is much more common than NPH and is the most probable cause of the so called "classical" triad. Although CT and MR imaging now facilitate the differentiation between subcortical arteriosclerotic encephalopathy and NPH, patients with subcortical arteriosclerotic encephalopathy are presumably still shunted for assumed NPH, especially when ventricular enlargement seems disproportionate to the degree of cerebral atrophy.

The main problem, however, is that, despite 30 years of experience, most of us still have management difficulties in patients presenting with communicating NPH who are considered to have a real albeit rather limited chance of improvement after a shunt on the basis of clinical and CT criteria. In this group the substantial benefit: serious harm ratio may be deceptively low, and labelling idopathic communicating NPH as a reversible dementia should be considered with extreme reserve.

In this group, disparities of practice remain high,
ranging from therapeutic nihilism to the pragmatic approach of shunting every patient suspected of NPH (“shunting the patient is the best test”). The urgent need for a simple, cheap, and accurate test for selecting the right patients for a shunt has been repeatedly uttered in review articles and editorials, and the quest is still under way. In the meantime, for clinicians with no access to ancillary investigations with a high predictive accuracy (almost all of us), the reasonable next step when doubts persist after assessment of the clinical, CT or MR, and CSF tap click, is to arrange a continuous external lumbar drainage for four to five days, and to shunt only patients with an unequivocal clinical improvement. In view of the low incidence of shunt responsive idiopathic NPH and the presumed high predictive accuracy of external lumbar drainage,\(^{11}\) the number of erroneous therapeutic decisions will probably be low and acceptably low. A multicentre prospective study assessing the validity and the reproducibility of this relatively simple diagnostic management is currently in progress in The Netherlands.

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NEUROLOGICAL STAMP

Charles Babbage (1792-1871)

The British mathematician Charles Babbage's interest in stimulating British scientific activity was not confined to mathematics. He founded the Royal Astronomical Society in 1820 and the Statistical Society in 1834, and he attacked the British public for their lack of interest in science. His inventions included a type of speedometer and the locomotive cow catcher. He contributed to the setting up of the British postal system in 1840 and compiled the first reliable actuarial tables. He is best known for his pioneering work in designing and building a mechanical computer.

Although he had theoretical insights into computer design, the prototype of his analytical machine was never completed due to the limitations of mechanical technology available and lack of money. The British Government finally funded his project financially, but then withdrew their support. Babbage put more and more of his own resources into the machine and in this he was assisted by Lord Byron's daughter, Ada, Countess of Lovelace who wrote a program for the analytical engine. With Lady Lovelace he devised a scheme for winning enormous sums of money on horse races but this was not a success and his financial situation continued to deteriorate. Eventually Babbage used up all his own money on the computer project. The incomplete prototype remains in the Science Museum in London. He was philosophically stripped by a storm issued by Great Britain in 1991 (Stanley Gibbons 1547, Scott 1361).