

CONTINUING MEDICAL EDUCATION

The Differential Diagnosis and Treatment of Normal-Pressure Hydrocephalus

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SUMMARY

Background: Normal-pressure hydrocephalus (NPH) arises in adulthood and is characterized by a typical combination of clinical and radiological findings. The mean basal intracranial pressure is normal or mildly elevated. The typical signs of the disease are gait impairment, urinary incontinence, and dementia. The difficulty of distinguishing NPH from other neurodegenerative disorders is the likely reason why some 80% of cases remain unrecognized and untreated. According to current evidence, the spontaneous course of NPH ends, for the vast majority of patients, in dependence on nursing care.

Methods: This review article is based on relevant publications retrieved by a selective search in Medline and on national and international guidelines for the management of NPH.

Results: Studies with a high evidence level are lacking; thus, the current state of knowledge about NPH is derived from studies of low or intermediate evidence levels, e.g., observational studies. Modern forms of treatment lead to clinical improvement in 70% to 90% of treated patients. The treatment of choice is the implantation of a ventriculo-peritoneal shunt. The differential diagnosis is complicated by the fact that three-quarters of patients with NPH severe enough to require treatment also suffer from another neurodegenerative disorder. Therefore, the clinical findings and imaging studies often do not suffice to establish the indication for surgery. To do this, a further, semi-invasive diagnostic procedure is recommended. Current risk/benefit analyses indicate that shunt operations improve outcome compared to the spontaneous course of the disease.

Conclusion: Normal pressure hydrocephalus should always enter into the differential diagnosis of patients who present with its characteristic manifestations. If the diagnosis of NPH is confirmed, it should be treated at an early stage.

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Normal-pressure hydrocephalus (NPH) was the first treatable type of dementia ever described and attracted much interest as soon as it became known.

S. Hakim described the entity he called normal-pressure hydrocephalus in 1963 (e1, e2). In the ensuing years, an initially uncritical enthusiasm for cerebrospinal fluid (CSF) shunting was gradually dampened because of the underdeveloped shunt technology then available, low clinical success rates, and frequent complications.

In the meantime, however, improved diagnostic and therapeutic methods have raised clinical success rates into the range of 70% to 90% (e3–e6), and risk-benefit analyses have shown beyond any doubt that surgery for NPH is far better than conservative treatment or the natural course (e7). This statement applies particularly to the idiopathic form of the entity (iNPH). Without surgery, the clinical state of patients with untreated iNPH generally worsens within a few months (e8), and their life expectancy is lower than if they were operated on (e7).

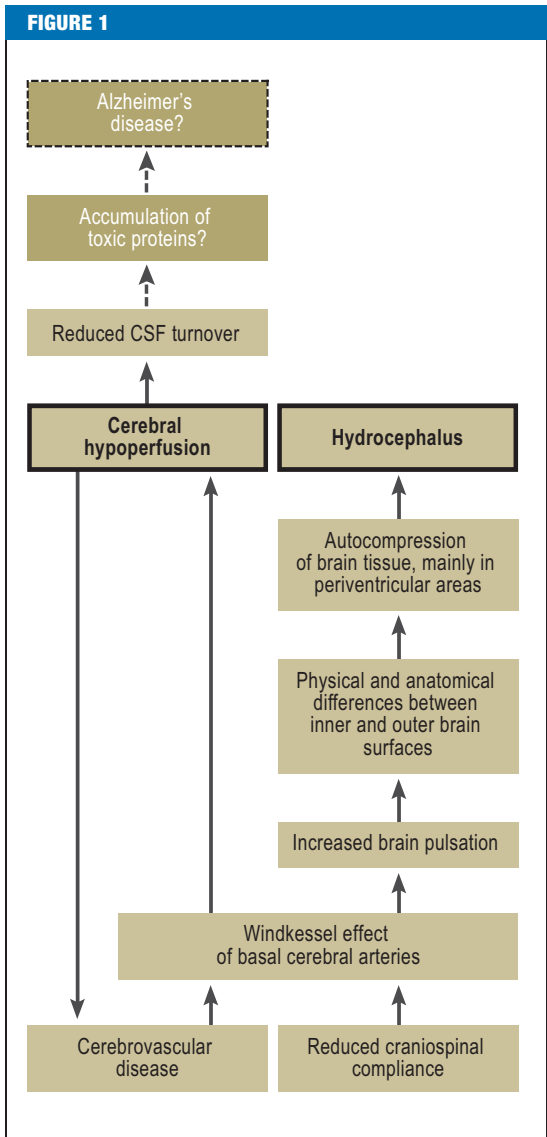
These facts make it all the more difficult to understand why, even today, only 10% to 20% of patients with NPH get the appropriate specialized treatment (e9–e11). We present an overview of the current state of the diagnosis and treatment of NPH.

Methods

This article is based on a selective review of the literature, including current guidelines from Germany and abroad (1–3), carefully selected review articles published since 2001, and original articles retrieved by a PubMed search. Levels of evidence were classified by the scheme used in international guidelines (e12).

Normal-pressure hydrocephalus

With modern diagnostic and therapeutic techniques, the rate of clinical improvement ranges from 70% to 90 %.



A current pathophysiological model of normal-pressure hydrocephalus
 According to the model, NPH results from low craniospinal compliance (intracranial reserve capacity) or low vascular compliance in the vessels of the circle of Willis. The model further postulates that the same causes can lessen cerebral blood flow and might also lead to Alzheimer's disease. It would thus account for the frequent simultaneous occurrence of NPH, Alzheimer's disease, and cerebral hypoperfusion.

There are no original publications providing level 1 evidence for the treatment of NPH. Therefore, this discussion is based on evidence of levels 2 and 3.

Learning aims

- After reading this article, the reader should be able to
- know the typical clinical and radiological features of normal-pressure hydrocephalus and how they differ from those of other diseases in its differential diagnosis,
 - know the current standards for the diagnosis and treatment of NPH, and
 - know that the mean clinical success rate of shunting is about 80%, and that treatment of NPH is indicated even in patients simultaneously suffering from other conditions of a neurodegenerative type.

Definition

Normal-pressure hydrocephalus is characterized by a combination of clinical and radiological findings arising in adulthood. The mean basal intracranial pressure (ICP) is normal or only mildly elevated (upper limit of normal in the supine adult: 15 mm Hg) (1, e13–e17).

The cardinal symptoms of NPH are gait impairment, dementia, and urinary incontinence. Imaging studies of the brain reveal ventriculomegaly without any marked degree of cortical atrophy (e15, e17, e18). In the absence of a generally accepted classification (e19), designations such as “communicating” or “malresorptive” hydrocephalus should be avoided, as these imply pathophysiological mechanisms whose role in NPH is not yet fully clear (e17, e18, e20).

Primary (idiopathic) normal-pressure hydrocephalus (iNPH) is distinguished from secondary normal-pressure hydrocephalus (sNPH) (e21), whose common causes are subarachnoid hemorrhage (23%), meningitis (4.5%), and traumatic brain injury (12.5%) (2). A common feature of iNPH and sNPH is that neither involves any obstruction to the flow of CSF within the ventricular system of the brain (e17, e22).

The basal ICP must be initially elevated, at least some of the time, for either iNPH or sNPH to develop (e17, e23). The two entities carry a similar prognosis (e6, e17, e24, e25). The only major clinical difference between them is that sNPH affects persons of all ages, while iNPH is a disease of the elderly (e20).

Definition

Normal-pressure hydrocephalus is characterized by a combination of clinical and radiological findings arising in adulthood.

Two types of NPH

Primary (idiopathic) normal-pressure hydrocephalus (iNPH) is distinguished from secondary normal-pressure hydrocephalus (sNPH).

The following discussion applies to NPH of either type, unless it is explicitly stated that what is said applies only to iNPH.

Epidemiology

In Germany today, one person in 80 is demented (e26–e29). About 250 000 persons receive a new diagnosis of dementia in Germany each year (4).

Normal-pressure hydrocephalus is thought to account for about 6% of all cases of dementia (e11, e20, e30, e31). A study of demented patients in nursing homes revealed that 9% to 14% of them had findings typical of NPH (e10).

The available epidemiological data are inconsistent, partly because of the lack of uniform diagnostic criteria. The incidence of NPH is estimated at anywhere from 0.2 to 5.5 new cases per 100 000 persons per year (e9, e32) (5–7). Its prevalence is reported to be 0.003% in persons under 65, and 0.2% to 2.9% for persons aged 65 or older (e9, e33, e34) (5–7). The prevalence of NPH, like that of the neurodegenerative conditions, rises markedly with age.

The differential diagnosis is complicated by the fact that 75% of patients with iNPH also have cerebrovascular dementia or Alzheimer’s disease. Studies have shown that 40% to 75% of patients with iNPH have beta-amyloid or other typical histological findings of Alzheimer’s disease, while 60% have signs of a cerebrovascular disease that could produce similar clinical findings to those of iNPH (e18, e35, e36) (8). In such patients, CSF shunting mainly improves gait, while cognitive improvement is less common (9, e18).

Pathophysiology

Various pathophysiological models of NPH have been proposed in the decades since its description. There is a consensus that the imbalance of CSF production and reabsorption in NPH is not due to overproduction, and that the resistance to CSF outflow (R_{out}) is often elevated (e37, e38). Particularly in the early phase of the disease, the intracranial reserve capacity appears to be low, as reflected by such measures as the craniospinal compliance or the pressure-volume index (PVI). It remains unclear, however, whether changes in compliance or R_{out} are contributory causes or simply epiphenomena of the condition. The frequent combination of NPH with cerebrovascular disease and Alzheimer’s disease makes it attractive to consider models in which these three entities are causally related (*Figure 1*) (1, 10); for

Pathophysiological models

The frequent combination of NPH with cerebrovascular disease and Alzheimer’s disease makes it attractive to consider models in which these three entities are causally related.

TABLE 1

Characteristics of gait impairment in NPH[†]

Feature examined	Clinical finding
Step frequency in 10 m gait test	Number of steps >13; duration >10 sec.
Step breadth	Distance between toes >1 foot length
Step length	Distance from heel of front foot to toes of rear foot <1 foot length
En bloc 360° turn	>4 to 6 steps
Bipedal gait	Correction of foot position in >25% of steps

[†]modified from (e17)

example, in one model, all three are caused by a loss of the Windkessel effect in the skull base arteries. This loss of elasticity may be either primary (e.g., due to atherosclerosis) or secondary, a consequence of low craniospinal compliance impeding the expansion of the arteries at the skull base. The result in either case is that higher compressive stress and greater shearing forces develop in the brain parenchyma (11, 12). Tissue damage and loss ensue mainly in the periventricular areas because of the physical and physiological differences between superficial and deep (periventricular) brain tissue (11, 12). This focal brain damage manifests itself as ventriculomegaly without any need to model a static pressure gradient from the inner to the outer CSF spaces. A further consequence of loss of the Windkessel effect is a lowering of cerebral blood flow, which explains the common simultaneous occurrence of iNPH and cerebral hypoperfusion; the latter, in turn, lowers CSF turnover. It has been hypothesized, but not yet shown, that low CSF turnover impairs the clearance of toxic metabolites and thereby contributes to the pathogenesis of Alzheimer’s disease.

Diagnosis and differential diagnosis

Clinical features

The clinical manifestations of NPH vary markedly; the rapidity and extent of the deterioration differ from one patient to another (e20). Impairments of gait and balance are typically the first symptoms to be noticed and may be very mild at the outset (e18). In the past, NPH was only diagnosed and treated when all three cardinal symptoms (the so-called “Hakim triad”) were demonstrably present (e17); the current recommendation,

Clinical features

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TABLE 2

**Differential-diagnostic criteria:
Similarities and differences of NPH and other neurodegenerative disorders**

Disease	Common features with NPH	Features that are atypical of NPH
Cortical dementias		
Alzheimer's disease	dementia without gait impairment is very rare	No gait disturbance until dementia is at least moderately severe; focal cortical deficits
Fronto-temporal dementia		Personality change, psychiatric abnormalities: disinhibition, impulsiveness, irritability, emotional lability; aphasia; no motor disturbance; incontinence very rare
Subcortical dementias		
Lewy-body dementia	Gait impairment and dementia	Visual hallucinations, delusions, markedly fluctuating cognitive function
Parkinson's disease and vascular parkinsonism	Hypokinetic gait, tremor (40%) in NPH (unilateral symptoms in NPH always indicate some type of comorbidity [e.g., cerebrovascular disease, Alzheimer's disease])	Rest tremor, unilateral onset; speed of movement can be increased with the aid of external stimuli (this is not the case in NPH). The patient cannot simulate walking and bicycle-riding while supine; no broad-based gait with externally rotated feet; mildly reduced step height, markedly reduced arm swing, markedly stooped posture, autonomic dysfunction
Progressive supranuclear palsy	Frontal brain signs, impaired executive function, gait disturbance	Pseudobulbar palsy, supranuclear upward gaze paresis
Corticobasal degeneration		Rigor, asymmetrical symptoms, alien-limb phenomenon, apraxia, supranuclear upward gaze paresis, cortical sensory deficits, severe loss of postural control
AIDS-dementia complex	Psychomotor slowing, impairment of memory and concentration, gait impairment due to HIV myelopathy	Positive HIV serology
Age-related depression	Pseudodementia, neuropsychological test findings very similar to those seen in NPH	Depressive thought content because of frequently comorbid vascular dementia, sometimes other features as well
Mixed dementias		
Vascular dementia	Thought disorder, impaired executive function	Asymmetrical (sometimes transient) symptoms, possibly correlated with lesions seen in imaging studies

however, is that NPH can be diagnosed and treated in the presence of only two cardinal symptoms (1–3), or even just one (e17, e18). This change in attitude resulted from the recognition that the prognosis worsens the longer NPH remains untreated (e39), with the complete Hakim triad always representing an advanced stage of the disease (e17). At present, 60% of NPH patients are demented at the time of shunting, and 50% are incontinent (e18).

Gait impairment

Impairments of gait and balance are the most common and, usually, the earliest symptoms of iNPH. They are also the most likely to improve after CSF shunting, with a probability of more than 85% (e15–e18). Patients may initially complain of dizziness, difficulty walking on a slope or stairs, and difficulty getting up from or sitting down on a chair.

As the disease progresses, the patient's gait deteriorates markedly, becoming broad-based, slow, short-stepped, and glue-footed (a gait disturbance of the abasia-astasia type) (2) (Table 1). Typical features of gait in NPH, of major importance for the differential diagnosis, are the following:

- Externally rotated posture of the feet
- Particular difficulty turning on the body's long axis
- Absence of apraxia.

In the late stage of NPH, the motor deficit is often worsened by the concomitant cognitive deficits, perhaps so severely that the patient is unable to walk at all.

Dysequilibrium in NPH is typically worse with the eyes closed, but patients need to stand on a broad base even when their eyes are open. The upper body is usually mildly stooped, but retropulsion can also be seen, either spontaneously or on provocation. Motor abnormalities in the upper limbs are mild or absent and generally restricted to bradykinesia.

Cognitive deficits/dementia

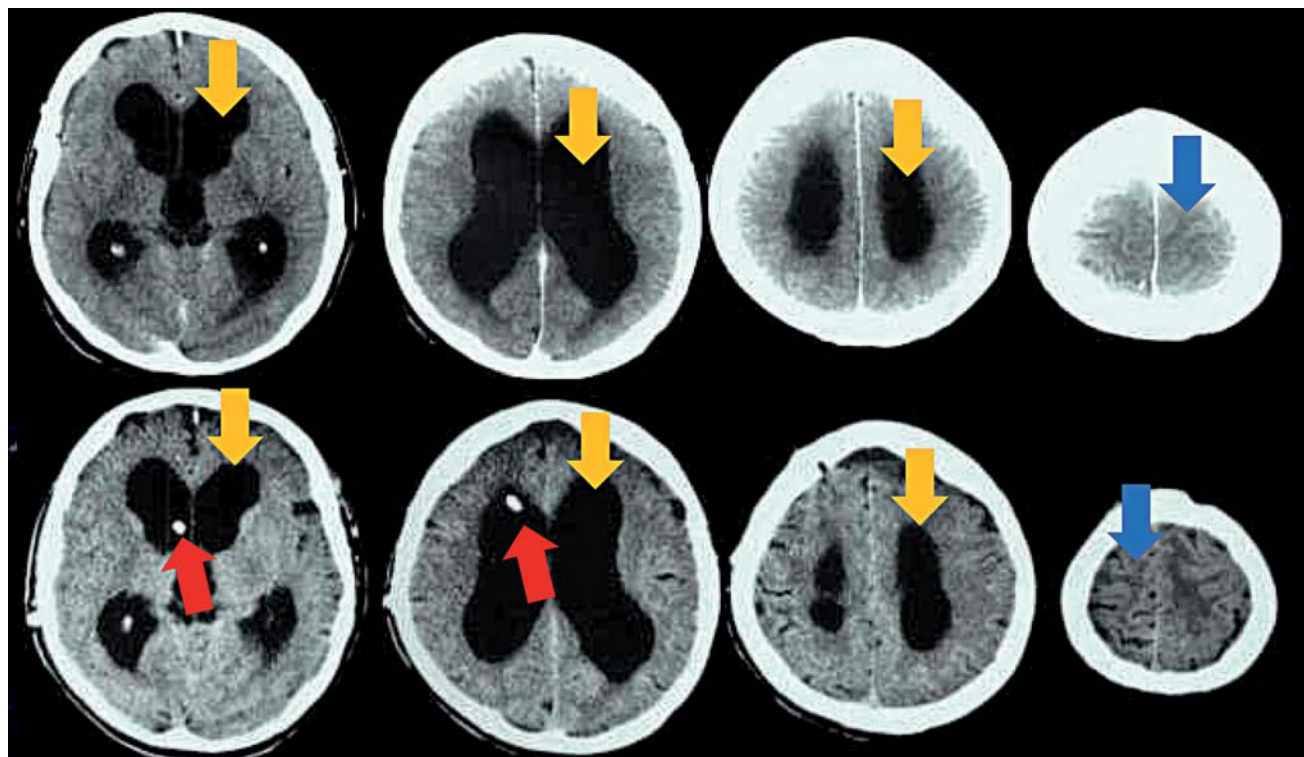
The cognitive deficits of iNPH are mainly due to subcortical frontal dysfunction. They affect executive functions first; thus, even early in the course of the disease, patients may have difficulty carrying out their everyday activities (e16–e18), while specific psychometric tests may still yield normal results. Later on, further deficits arise, at least two of which must be present for the diagnosis of a cognitive deficit/dementia to be made (13, e16–e18):

Gait impairment

Patients may initially complain of dizziness, difficulty walking on a slope or stairs, and difficulty getting up from or sitting down on a chair.

Differential diagnostic criteria

- Externally rotated posture of the feet
- Difficulty turning on the body's long axis
- Absence of apraxia



Photographs: Neurology Dept., Universitätsklinikum des Saarlandes

Figure 2: Cranial CT of a patient with normal-pressure hydrocephalus before and after CSF shunting (upper and lower rows, respectively). Yellow arrows: There is hardly any change of ventricular size after shunting. The change may be very small or not noticeable at all at first glance. Blue arrows: After shunting, the CSF spaces over the convexity near the vertex are wider; this is the sole reliable sign of adequate CSF drainage through the shunt. Red arrows: The tip of the ventricular catheter lies in the right frontal horn.

- Psychomotor slowing
- Impaired attention and concentration
- Slowing and reduced precision of fine motor performance
- Short-term memory impairment (new information can be taken in, but not repeated)
- In the late stage: apathy, reduced drive, indifference, bradyphrenia, reduced speech production (rarely, akinetic mutism).

Aside from reactive depression (without depressive thought content) (e16–e18), patients with NPH generally do not have any psychiatric abnormalities. Thus, changes of mood, personality, and behavior steer the differential diagnosis toward a neurodegenerative disorder of another type. An objective examination

should be performed with the aid of specific psychometric tests for the assessment of subcortical frontal lobe deficits.

Some suitable tests of this type are (e40, e41):

- the grooved pegboard test
- the Stroop test
- the digit span test
- the trail-making A/B test
- the Rey auditory-verbal learning test

On the other hand, the Mini-Mental Status Test and the DEMTEC Test are unsuitable, as they were developed for cortical dementias (13, 14).

Early CSF shunting can still improve the cognitive deficits in as many as 80% of patients with iNPH, but improvement is less likely if the patient simultaneously has vascular or Alzheimer’s dementia.

Most common deficits leading to the diagnosis of cognitive impairment/dementia:

- Psychomotor slowing
- Impaired attention and concentration
- Fine motor slowing and imprecision
- Short-term memory impairment

Suitable neuropsychological tests:

Grooved pegboard test, Stroop test, digit span test, trail-making A/B test, Rey auditory-verbal learning test

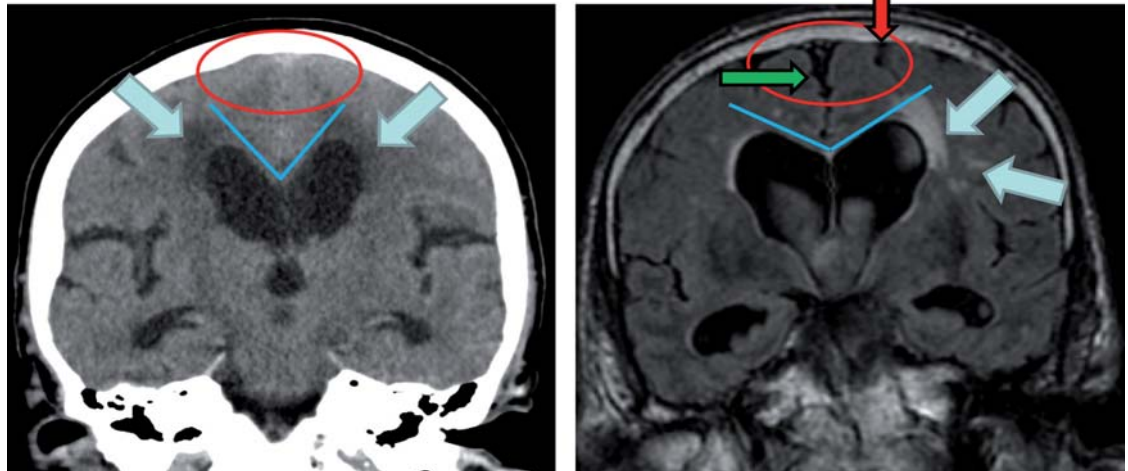


Figure 3: Coronal head CT (left) and MRI (right) at the level of the posterior commissure: on the left image, the CSF spaces over the convexity near the vertex are narrowed (“tight convexity,” red circle), as are the medial cisterns (red circle)—these are typical findings of NPH. On the right image, however, the CSF spaces over the convexity near the vertex (red arrow) and the medial cisterns (green arrow) are widened, a finding consistent with brain atrophy. The blue lines in both images indicate the callosal angle: an angle less than 90° is typical of NPH (left image), while an angle greater than 90° is typical of brain atrophy (right image). The blue arrows indicate periventricular signal alterations. Their unilateral occurrence (right image) suggests that they are probably due to vascular encephalopathy. The abnormalities seen on the left image may well represent transependymal CSF diapedesis due to NPH

Photographs: Neuroradiology Dept., Universitätsklinikum des Saarlandes

Incontinence

Disturbances of bladder function in NPH result from detrusor hyperactivity owing to the partial or total absence of central inhibitory control. Patients initially suffer from increased urinary frequency (e42–e44); later developments are urge incontinence and, finally, permanent urinary incontinence. Fecal incontinence is rare in NPH (2) and should arouse suspicion of another type of neurodegenerative disease. If present in a patient with NPH, it implies severe frontal subcortical dysfunction.

CSF shunting can improve bladder dysfunction in as many as 80% of iNPH patients if performed early, but in no more than 50% to 60% if performed in an advanced stage of the disease (e15, e20, e45).

Differential diagnosis

Many elderly people suffer from combined motor and cognitive dysfunction (and sometimes from incontinence as well). Moreover, three-quarters of patients with (i)NPH simultaneously have vascular or Alzheimer’s dementia. Thus, the differential diagnosis

of NPH can be quite difficult. Findings that make the diagnosis of NPH less likely include the following:

- Intracranial pressure above 25 cm H₂O (this rules out iNPH, by definition)
- Age under 40 (iNPH unlikely)
- Asymmetrical or transient symptoms
- Cortical deficits, e.g., aphasia, apraxia, or paresis
- Progressive dementia without gait disturbance (even if the ventricles are enlarged)
- Lack of progression of symptoms (a controversial point, as authors differ on the period of time in which symptoms should be seen to progress).

The differential diagnosis of gait disturbances includes peripheral neuropathy, spinal canal stenosis, disorders of the inner ear, chronic alcoholism, and deficiencies of vitamin B6 and B12 (2, e17, e18). The differential diagnosis of cognitive deficits includes various types of dementing disease (Table 2). It is often not possible to distinguish NPH from other causes of subcortical dementia by the clinical and radiological findings alone, so that further, invasive tests are needed (e17, e18, e20, e45).

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Findings that make NPH less likely:

- Asymmetrical findings
- Cortical deficits, e.g., aphasia, apraxia, paresis
- Progressive dementia without gait disturbance
- Lack of progression of symptoms

Imaging studies and other noninvasive diagnostic techniques

Either computerized tomography (CT) or magnetic resonance imaging (MRI) of the brain is necessary—yet, alone, never sufficient—to establish the diagnosis of NPH.

Typical findings of NPH include disproportionate widening of the ventricles in comparison to the cerebral sulci (inner vs. outer CSF spaces; see *Figure 2*) (1). A coronal section at the level of the posterior commissure reveals a narrow subarachnoid space surrounding the outer surface of the brain (a “tight convexity”) and narrow medial cisterns (*Figures 3 and 4*) (e46–e48). The third ventricle is usually enlarged as well, while the fourth ventricle may or may not be enlarged (*eFigure 1*) (11). Thus, a fourth ventricle of normal size in the presence of enlarged lateral and third ventricles need not indicate aqueductal stenosis and is a finding consistent with NPH (11). Changes in the signal characteristics of periventricular tissue must be interpreted with caution (*eFigure 2*): subcortical vascular encephalopathy (SVE) may cause changes quite similar to those seen in NPH as a result of transependymal CSF diapedesis. Yet, the presence of SVE still does not rule out concurrent NPH that might improve with treatment (e49–e52). It would be a serious error in such cases to ascribe all symptoms to SVE alone, thereby depriving the patient of the chance of therapeutic benefit from CSF shunting (e50, e51).

Further imaging modalities to assess cerebral blood flow and metabolism or of CSF dynamics (PET, SPECT, scintigraphy, CSF biomarkers, and newer functional MRI techniques) so far play no role in routine clinical evaluation (1–3).

Invasive diagnostic testing

The clinical and radiological findings, taken together, have only limited prognostic value (e12). Particularly in patients with iNPH, further testing is needed to raise the prognostic accuracy above 80% (1–3):

- Spinal tap test: lumbar puncture with the removal of 30 to 70 mL of CSF. This can be repeated on two or three consecutive days.
- Continuous spinal drainage of 150 to 200 mL of CSF per day for 2 to 7 days (1–2).

We consider such tests to be positive if the number of steps taken in a 10 m gait test, and the time needed to walk 10 m, are reduced by at least 20%, and/or psychometric tests show an improvement of at least 10%.

- Alternatively, certain features of CSF dynamics (R_{out} , compliance) can be measured with infusion tests (*Figure 5*) (15, 16).

In Germany, unlike the rest of continental Europe, the United Kingdom, and the United States, the measurement of CSF dynamics has not yet become established in all centers. It is nonetheless recommended in the current guidelines of the German Neurological Society (*Deutsche Gesellschaft für Neurologie*), just as it is in the foreign guidelines (1, 2). Risk-benefit analyses have shown all three techniques to be of equivalent value (e12); thus, each center should use the one with which it has the most experience (2). Further testing with the other techniques is indicated only if the findings are inconclusive.

Other invasive tests

Long-term ICP measurement for 24 to 72 hours is performed in no more than a few centers. Special pressure waves and brain pulse amplitudes are measured (16, e53). Such techniques are not recommended for routine use, both because their predictive value has not yet been sufficiently documented and because they require specialized equipment and expertise (16).

Treatment

No prospective, double blind, randomized, controlled clinical trials of the treatment of NPH have been performed to date. It is hard to collate the findings of the available observational studies and draw conclusions from them, because, even today, the clinical findings before and after treatment are assessed with a wide variety of measures, and the potential complications are not uniformly defined. It is harder still to compare current results with historical data, because the assessment of clinical outcomes and complications was even less well-defined in the past. Thus, if we speak of “clinical improvement” and complications in what follows, then only while remaining aware of the heterogeneity of these entities. Nevertheless, despite all of the difficulties in evaluating the data, the authors’ experience and their overall impression of the literature point to a marked improvement in clinical outcomes along with a reduction of complications in the past ten years. There is certainly no longer any justification for therapeutic nihilism.

The standard treatment of NPH is the implantation of a ventriculoperitoneal (VP) shunt. Ventriculo-atrial (VA) shunts were implanted in the past but have fallen

Imaging studies

Either cranial computerized tomography (CT) or magnetic resonance imaging (MRI) of the brain is necessary—yet, alone, never sufficient—to establish the diagnosis of NPH.

Invasive diagnostic testing

Particularly in patients with iNPH, invasive testing is needed to increase the prognostic accuracy to 80% or more.

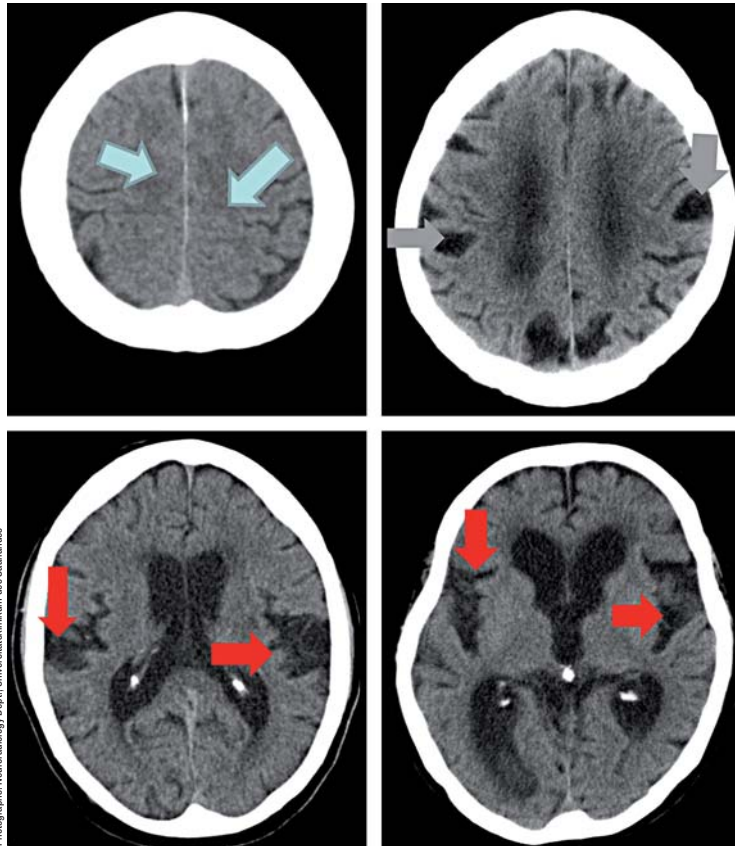


Figure 4: Typical cranial CT of a patient with iNPH. The CSF spaces near the vertex are narrow (blue arrows); the few wide sulci that are seen on the cerebral convexity (gray arrows) are all in the vicinity large, superficial arteries. Widening of the insular cisterns (red arrow) is a good indicator of iNPH that will respond to treatment

Photographs: Neurosurgery Dept., Universitätsklinikum des Saarlandes

out of use, except in rare cases, because of their more frequent long-term complications (1, 2, 17). In the English-speaking countries, lumboperitoneal (LP) shunts are also implanted to treat NPH (1). For the great majority of patients with NPH, endoscopic third ventriculostomy (ETV) is not a suitable therapeutic option (18, e54); it is one only for those with a locally confined, infratentorial, extraventricular obstruction to CSF flow (e55–e57). Such an obstruction is typically characterized by a protrusion of the lamina terminalis and the floor of the third ventricle into the adjacent basal cisterns (e54), which can be seen on close inspection of the MR images. Carbonic anhydrase inhibitors

and serial lumbar punctures are not advisable as alternative treatments (e58), except for a limited time in medically inoperable patients.

The current guidelines favor the use of adjustable shunt valves in the treatment of iNPH (1–3, 20). The option of adjusting the valves' opening pressure noninvasively enables fine tuning of the ventricular drainage, potentially obviating the need for reoperation (e59–e61). Unlike their earlier counterparts, adjustable valves of the most recent generation cannot be unintentionally reset when subjected to magnetic fields of up to 3 T (20). It remains to be seen, however, whether they are as robust as simple differential-pressure valves.

The main advance of the past two decades has been the introduction of gravity-controlled valves (G valves). A low valve opening pressure when the patient is lying down is an important factor in therapeutic success, particularly in iNPH (21, e37, e38, e63). Such a low pressure would, however, be associated with a high risk of overdrainage in a mobile patient if a G valve were not implanted (21, e37, e38, e64), and this problem is still not fully solved by the use of an adjustable valve (e64). G valves enable a low valve opening pressure when the patient is lying down without elevating the risk of overdrainage (e64). Their opening pressure is mainly controlled by gravity: they present a lower resistance to CSF flow when horizontal than when vertical. Thus, when the patient changes position, the outflow resistance in the valve changes in tandem with the hydrostatic pressure gradient of CSF. As shown in the SWASONA study, G valves lower the risk of overdrainage by 90% without impairing the efficacy of treatment (e37, e64). They may, therefore, be particularly suitable for use in mobile patients with iNPH.

On the other hand, in bedbound NPH patients, the hydrostatic CSF pressure gradient hardly ever changes, and a simple and robust differential-pressure valve may well be the better choice (e62). Patients with secondary NPH of known cause and recent onset are also often well served with a simple differential-pressure valve.

Clinical outcome

It is currently reported that 70% to 90% of patients with NPH (including iNPH) obtain a lasting clinical benefit from shunting compared to their preoperative state, with follow-up intervals ranging from one to seven years (e59, e61, e64, e66–e69). This is a marked improvement over the therapeutic outcomes seen in the past (e44, e65).

Long-term ICP measurement

Long-term ICP measurement is not recommended for routine use, both because its predictive value has not yet been sufficiently documented and because it requires specialized equipment and expertise.

The standard treatment of NPH

The standard treatment of NPH is the implantation of a ventriculoperitoneal (VP) shunt.

Today, one can even see an improvement in all three domains of the Hakim triad, compared to the patients' preoperative state, in more than 80% of patients after seven years of follow-up (e70, e71). In some patients, however, the initial improvements of cognitive function and bladder control subside again over the next few years (e68). This secondary deterioration is presumed to reflect the progression of concomitant neurodegenerative disease (e6, e65, e72).

Complications

Modern materials (22, 23) and valve designs (9) have lowered the rate of shunt-related complications (failure 3%, over/underdrainage or subdural hematoma 3% to 4%, infection <1%); as a result, their overall long-term prevalence is less than 20% (21, 22, e60, e64, e67, e73). Thus, the mean complication rates of 35% to 40% reported in the past (24, e44) have been halved. Complications unrelated to shunting, such as epileptic seizures and intracerebral hemorrhage, occurred in 6% to 14% of patients in the past (19, e44) but are now encountered in less than 5% (e60, e64, e67, e73). It was pointed out years ago already that shunt complications, when they occur, only rarely leave lasting damage or impair the therapeutic outcome (19). There have been no perioperative deaths at all in the more recent clinical series (19, e15–e18, e53, e60, e64, e67). Overall, it is now clear that CSF shunting to treat NPH carries a perioperative severe morbidity of less than 5% and a mortality of less than 1%; these are safe estimates, assuming that not all of the complications that actually occurred were captured in the published studies (9).

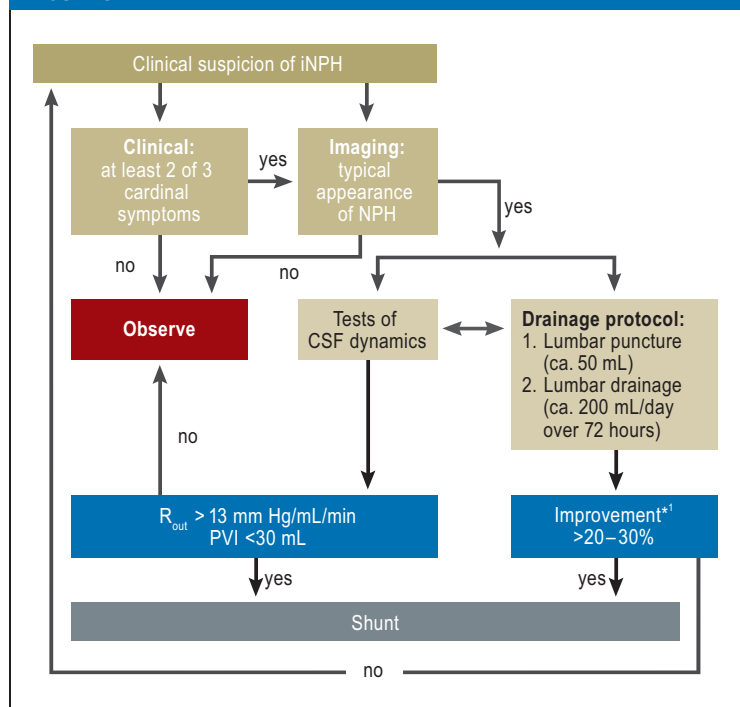
The most convincing argument in favor of surgery comes from a risk-benefit analysis performed with the aid of a Monte Carlo simulation model (e7, e8), which led to the conclusion that shunt implantation yields far better results than conservative management (e7).

Follow-up management after shunting

Two to three postoperative follow-up visits are advisable in the first year after shunting (e74), as this is when complications tend to arise (24). Patients with an uncomplicated course can be followed up thereafter at longer intervals (1 to 3 years). Patients who have had shunt failures and infections in the past should be followed up more often, as they are more likely to have further complications (e74).

Aside from the physical examinations performed in routine clinical follow-up, cerebral imaging should be

FIGURE 5



Diagnostic flowchart. If NPH is suspected on clinical and radiological grounds, diagnostic accuracy can be secured with invasive testing (CSF drainage or measurement of CSF dynamic variables such as compliance and resistance to outflow). Such tests are often needed for adequate confirmation of the indication for shunting, particularly in patients with iNPH.

*1 In the 10 m gait test, at least 20% improvement; in psychometric tests, at least 10% improvement.
PVI, pressure-volume index; R_{out}, resistance to outflow.

performed at some point during the first year after shunting and a few weeks after any resetting of the opening pressure of adjustable valves. No more imaging studies need be performed after that, except in case of clinical worsening or as indicated by the patient's individual risk profile. Patients with VA shunts should have regular testing of their C-reactive protein concentration (17, 25) (particularly in the first year after surgery) and of their D-dimers for the early detection of subclinical chronic septicemia and/or thromboembolism. D-dimer monitoring obviates the need for transesophageal echocardiography. There is no need at all for routine "shunt pumping": This practice should be abandoned, as the large positive and negative

Local obstruction to CSF flow

Such obstructions are typically characterized by protrusion of the lamina terminalis and the floor of the third ventricle into the adjacent basal cisterns.

Clinical outcome

70% to 90% of patients with iNPH experience clinical improvement after CSF shunting.

pressure changes that it creates can destroy the shunt valve or lead to partial aspiration of the choroid plexus into the ventricular catheter, with occlusion of the latter. A very important point for postoperative imaging is the following: In the past, a marked reduction of ventriculomegaly was considered to be a sign of adequate drainage. After G valves were introduced, it became clear that such a dramatic narrowing of the ventricles is unnecessary for therapeutic success (e66) and is, rather, an expression of (latent) overdrainage (2, 9, 20). When a G valve is used, the ventricles may become only a little bit narrower despite therapeutically adequate drainage. The only reliable sign of adequate drainage in a CT or MR image is a freer subarachnoid space in the vicinity of the vertex-near cisterns, compared to the preoperative image (Figure 2).

Overview and perspective

In the past two decades, innovative valve techniques have led to marked improvements in CSF shunt therapy. Coming electronic and mechatronic innovations in shunt technology may bring about further improvement.

The authors' research teams are currently working on an ICP telemetry project (eFigure 4). We have been performing telemetric shunt checks for the last two years; in future, they may become part of routine clinical practice.

Conflict of interest statement

Prof. Unterberg states that he has no conflict of interest.

Prof. Kiefer has received honoraria and/or financial support for consulting activities and for the preparation and scientific direction of continuing education meetings, as well as reimbursement of travel costs and participation fees for scientific conferences, with the approval of each of these outside activities by his main employer (Universitätsklinikum des Saarlandes), from the following firms: Aesculap AG (Tuttlingen, Germany), a subsidiary of B. Braun AG (Melsungen, Germany); Miethke KG & Co KG (Potsdam, Germany); Raumedic AG (Helmbrechts, Germany); and Codman AG (Norderstedt, Germany), a subsidiary of Johnson & Johnson (New Brunswick, USA). He has also purchased a small number of newly developed products at reduced prices from some of the above-named companies for a short time only, by agreement between his main employer and the companies, in order to test these products personally in his routine clinical work. He has received honoraria, reimbursement of expenses, and some reimbursement of travel fees from Codman AG, Aesculap AG, and ASKLEPIOS-proresearch (Hamburg) for the performance of investigator-initiated clinical studies, after approval by his main employer.

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Further management

Two to three postoperative follow-up visits are advisable in the first year after shunting, as this is when complications tend to arise. Patients with an uncomplicated course can be followed up thereafter at longer intervals (1 to 3 years).

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The solutions to the following questions will be published in issue 9/2012.

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Please answer the following questions to participate in our certified Continuing Medical Education program. Only one answer is possible per question. Please select the answer that is most appropriate.

Question 1

What are the cardinal symptoms of idiopathic normal-pressure hydrocephalus (iNPH)?

- a) Apathy, tremor, and rigidity
- b) Reduced muscle tone, urinary and fecal retention, and dementia
- c) Gait impairment, incontinence, and dementia
- d) Gait impairment, tremor, and akinesia
- e) Difficulty initiating gait, affect incontinence, organic brain syndrome

Question 2

What changes on imaging studies (computerized tomography [CT], magnetic resonance imaging [MRI]) are the most characteristic of normal-pressure hydrocephalus (NPH)?

- a) Disproportional width of inner and outer CSF spaces
- b) Marked atrophy of the frontal lobes
- c) Lack of periventricular signal changes or hypodensities
- d) Enlargement of both inner and outer CSF spaces
- e) Enlargement of inner CSF spaces, narrowing of outer CSF spaces on the skull base solely

Question 3

What constellation of changes in imaging studies (CT, MRI) definitively establishes the diagnosis of NPH?

- a) Narrow cisterns near the vertex and a callosal angle $<90^\circ$
- b) Enlarged insular cisterns and inner CSF spaces
- c) Enlarged insular cisterns and narrow cisterns near the vertex
- d) A callosal angle $<90^\circ$ and enlarged inner CSF spaces
- e) There is no such constellation of changes

Question 4

What ancillary tests are often needed to confirm the indication for CSF shunting, especially in patients with iNPH?

- a) An infusion test or a scintigraphic study of the CSF spaces
- b) Glucose-PET and diffusion-weighted MRI
- c) MR spectroscopy and a spinal tap test or continuous lumbar CSF drainage
- d) A spinal tap test, continuous lumbar CSF drainage, or an infusion test
- e) Specific psychometric testing after an infusion test

Question 5

What percentage of patients with iNPH also have vascular dementia or Alzheimer's disease?

- a) 15%
- b) 30%
- c) 45%
- d) 60%
- e) 75%

Question 6

According to epidemiological studies, how common is iNPH?

- a) In the elderly, its incidence is 6%, and its prevalence has been estimated with figures ranging from 12% to 18%.
- b) It accounts for about 6% of all cases of dementia, and its prevalence among the elderly has been estimated with figures ranging from 0.2% to 2.9%.
- c) Its incidence is 0.3% and its prevalence is 0.8% (average figures for all age groups).
- d) Its prevalence among the elderly is about 6%.
- e) Its prevalence among persons under age 65 is between 0.2% and 2.9%.

Question 7

What is the standard treatment of NPH?

- a) Ventriculoperitoneal shunting
- b) Diuretics
- c) Endoscopic third ventriculostomy
- d) Serial lumbar punctures
- e) Lumboperitoneal shunting

Question 8

What was the conclusion of risk-benefit analysis of the treatment of NPH that employed a Monte Carlo simulation model?

- a) Shunting is markedly superior to conservative management.
- b) Drug treatment markedly lowers basal intracranial pressure (ICP) and improves the quality of life.
- c) Shunting lowers the quality of life.
- d) There has been an increase in perioperative mortality.
- e) The overdrainage rate has gone down by about 20%.

Question 9

Which of the following statements about the clinical course of NPH after shunting is correct?

- a) Shunting has no effect on life expectancy.
- b) Shunting generally has no effect on the course of the disease.
- c) Rapid progression and clinical deterioration are the rule.
- d) Shunting generally shortens life expectancy.
- e) In patients with NPH who have no other comorbid conditions, shunting can arrest the progression of the disease.

Question 10

As a rule, what type of follow-up should patients have in the first year after CSF shunting?

- a) Monthly cranial CT or MRI
- b) Two to three clinical follow-ups and imaging study.
- c) Bimonthly imaging studies.
- d) Mini-Mental Status Tests every three months.
- e) Biannual DEMTEC tests.