Normal Pressure Hydrocephalus

By Neill R. Graff-Radford, MBBCH, FRCP, FAAN; David T. Jones, MD

REVIEW ARTICLE

CONTINUUM AUDIO INTERVIEW AVAILABLE ONLINE

VIDEO CONTENT AVAILABLE ONLINE

ABSTRACT

PURPOSE OF REVIEW: **Since it was first described in 1965, normal pressure hydrocephalus (NPH) has been a controversial subject. New studies have shed light on its epidemiology and pathogenesis and provided objective ways to measure outcome in patients with NPH. Neuroimaging has improved and allows better recognition of both NPH and the presence of overlapping diseases**

RECENT FINDINGS: **Several recent epidemiologic studies confirm that NPH is a rare disease, but the presence of large ventricles is a common finding with aging. NPH may be multifactorial, including congenital causes, vascular disease, and impaired CSF absorption. MRI features of NPH include enlarged ventricular size and CSF fluid collection outside the ventricles not due to atrophy. The term *disproportionately enlarged subarachnoid space hydrocephalus* (DESH) has been used to describe prognostic MRI features in NPH, including a "tight high convexity" and enlargement of CSF spaces in the sylvian fissure. DESH has been included in the Japanese guideline for the diagnosis and treatment of NPH. A new NPH scale has been published that provides an objective framework for evaluating patients with NPH before and after shunt placement. Programmable shunts can noninvasively manage overdrainage complications. Surgical outcome has been improving over time. Recent studies have led to improved recognition of overlapping diseases such as Alzheimer pathology, which co-occurs in about 30% of NPH cases. Fludeoxyglucose positron emission tomography (FDG-PET) is a promising imaging modality for diagnosing NPH and detecting concomitant degenerative disease.**

SUMMARY: **A systematic approach to patients with possible NPH allows recognition of the subset of patients who will respond to shunt surgery and identification of those with alternative diagnoses.**

INTRODUCTION

Adams and colleagues[1] published the first article on normal pressure hydrocephalus (NPH) in 1965 based on Hakim's hypothesis that patients with hydrocephalus but normal CSF pressure on lumbar puncture (LP) could improve with shunt surgery. Two key guidelines have been published on NPH, the international guideline[2] and the Japanese guideline.[3] The American Academy of Neurology practice guideline on NPH concluded that clinicians may offer shunt placement

CITE AS:
CONTINUUM (MINNEAP MINN) 2019;25(1, DEMENTIA):165–186.

Address correspondence to Dr Neill R. Graff-Radford, Department of Neurology, Mayo Clinic Jacksonville, 4500 San Pablo Rd, Jacksonville, FL 32224, *Graff-radford.neill@mayo.edu*.

RELATIONSHIP DISCLOSURE:
Dr Graff-Radford serves on the editorial board of *Alzheimer's Research & Therapy* and receives research/grant support from Abbvie Inc; Axovant Sciences, Inc; Biogen; Eli Lilly and Company; the National Institutes of Health (P50AG16574, 1R01AG045390-01A1, R56AG057195, UF1AG032438, U54NS092089, U01AG24904, U01NS100620); Novartis AG; and the US Department of Defense (WE11872). Dr Jones receives research/grant support from the Minnesota Partnership for Biotechnology and Medical Genomics (P006598701) and the National Institutes of Health (U01EB 24450-1, R01DC14942-1, U01AG52943, U01AG45390, U19AG24904).

UNLABELED USE OF PRODUCTS/INVESTIGATIONAL USE DISCLOSURE:
Drs Graff-Radford and Jones report no disclosures.

as a treatment for patients with idiopathic NPH to treat their subjective symptoms of idiopathic NPH and gait with Level C evidence but recommended that additional well-designed randomized clinical trials are needed for NPH.[4]

Two recent randomized studies have been published on NPH. In the first trial,[5] a group of patients with NPH was shunted immediately with a lumboperitoneal shunt and compared to a control group of patients with NPH who underwent lumboperitoneal shunt surgery after a 3-month delay. At 3 months, only 5% of the delayed shunt group improved compared to 65% of the immediately shunted group as measured by the modified Rankin Scale (mRS). Tisell and colleagues[6] completed the only double-blind randomized study in NPH. Among 14 patients with NPH, vascular risk factors, and no absorption problem, seven participants had their shunts open immediately after surgery, while the other seven had their shunts tied closed for 3 months. The group who had their shunts open improved immediately, and the second group improved only when their shunts were opened 3 months later.

Although limited by size, these two studies provide additional evidence of the efficacy of shunt surgery for NPH, but a large double-blind study is still necessary before practice guidelines can recommend shunt surgery with a higher level of confidence. Because of the lack of a large randomized double-blind study, the treatment of patients with NPH has been questioned by some, including in a 2016 editorial.[7]

This article provides a practical approach to the management of NPH and reviews NPH nomenclature, etiology, epidemiology, clinical findings, and the approach to diagnosis, including for complicated cases with overlapping diseases. Recent advances in MRI diagnosis are highlighted, and surgical considerations, how to evaluate shunt outcome, and the prognosis of patients undergoing shunt surgery are discussed.

NORMAL PRESSURE HYDROCEPHALUS NOMENCLATURE

CSF is produced in the choroid plexuses of the ventricular system at a rate of 20 mL per hour and flows from the lateral and third ventricles to the fourth ventricle via the cerebral aqueduct. The fourth ventricle communicates with the subarachnoid space via the midline foramen of Magendie and the two lateral foramina of Luschka. The CSF then circulates through the subarachnoid space over the cranial convexity and down the spinal canal before being reabsorbed by arachnoid villi located along the intracranial venous sinuses and around the spinal nerve roots. CSF is circulated through the ventricular and subarachnoid spaces by a pulsatile wave induced by the expansion of the vascular compartment within the rigid cranial vault associated with pulsatile flow in the cerebral arteries. In healthy adults, the CSF volume is between 125 mL and 150 mL, with 20% residing in the ventricular system and the remainder in the cerebral (approximately 65%) and spinal (approximately 15%) subarachnoid spaces.

The term *hydrocephalus* is a compound word with origin from the Greek words for water (*hýdōr*) and head (*kephalos*). In modern medical usage, the term is meant to capture the clinical condition of increased CSF content within the cranial vault caused by a variety of circumstances.

While the ventricular system is a common and salient location for increased CSF content within the cranial vault, it should be emphasized that the term *hydrocephalus* also encompasses increased CSF content in the extraventricular cranial subarachnoid space. The term *ventriculomegaly* is used to describe

increased CSF content in the ventricular system and the term *subarachnoid hydrocephalus* to describe increased CSF content in the cranial portion of the subarachnoid space.

KEY POINT

● Hydrocephalus can occur as fluid accumulation both inside and outside the ventricles.

ETIOLOGY

The following sections discuss factors that relate to NPH, including congenital factors, poor CSF absorption, and vascular factors.

Congenital Factors

Traditionally, hydrocephalus has been divided into two broad categories: obstructive and communicating. Obstructive hydrocephalus, also known as noncommunicating, is secondary to a blockage of the normal CSF flow through the ventricular and subarachnoid spaces associated with a congenital condition or acquired with the development of a brain lesion that exerts obstructive mass effect. Stenosis of the cerebral aqueduct is a common cause of hydrocephalus in the young, but symptoms may not manifest until adulthood and may account for the syndrome *long-standing overt ventriculomegaly in adults* (LOVA), which has a clinical presentation similar to NPH (dementia, gait disturbance, and urinary incontinence). The authors and others have shown that persons diagnosed with NPH have a large head size in more than 10% of cases (eg, 20% have a head size larger than the 90th percentile),[8,9] supporting that congenital factors may play a role in the development of hydrocephalus even in adulthood. Secondary NPH may be suspected in the setting of a large head size, triventriculomegaly without involvement of the fourth ventricle, little to no T2 signal change around the ventricular system on fluid-attenuated inversion recovery (FLAIR) imaging, and evidence of aqueductal stenosis and/or webbing identified with special MRI sequences (refer to the MRI section) of the cerebral aqueduct (FIGURE 8-1).

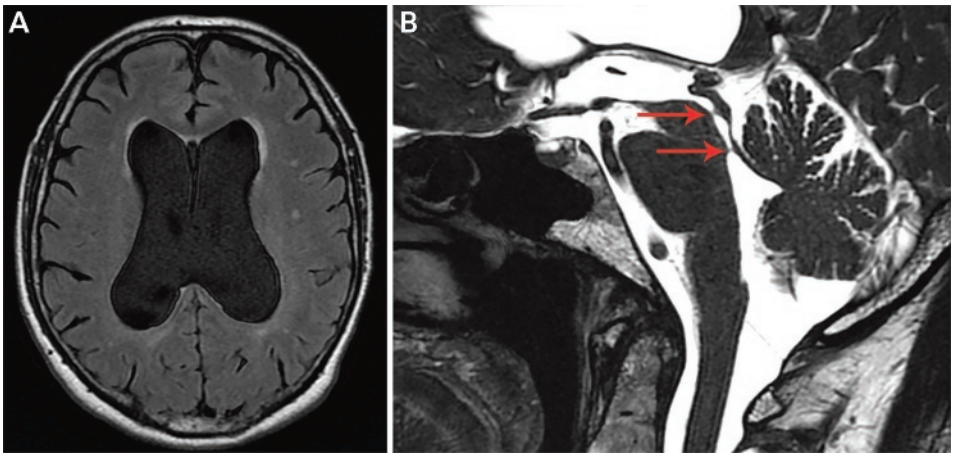

FIGURE 8-1

Long-standing overt ventriculomegaly in adults (LOVA). *A*, Axial fluid-attenuated inversion recovery (FLAIR) MRI sequence shows ventriculomegaly without significant T2 signal around the ventricles. A lack of subarachnoid hydrocephalus suggests a noncommunicating etiology for the ventricular hydrocephalus. *B*, Sagittal fast imaging employing steady state acquisition C (FIESTA-C) sequence in the same patient shows two membranes/webs (*arrows*) within the cerebral aqueduct leading to stenosis and partial obstruction.

In contrast to obstructive hydrocephalus, communicating hydrocephalus is characterized by an increase in intracranial CSF content without a gross anatomic lesion obstructing flow. NPH, the topic of this article, is a form of communicating hydrocephalus that occurs insidiously without substantially increasing CSF pressure. The NPH syndrome can be primary, ie, without a known cause (referred to as *idiopathic NPH*), or secondary to some condition that is known to impair CSF absorption at the arachnoid granulations (eg, following infectious, inflammatory, or hemorrhagic events involving the subarachnoid space). Similar to obstructive hydrocephalus, the clinical symptoms associated with primary and secondary forms of NPH are responsive to surgical treatment (eg, ventriculoperitoneal shunt, ventriculopleural shunt, lumboperitoneal shunt, or some other surgical CSF diversion procedure).

Cerebrospinal Fluid Absorption Impairment

The mechanisms that lead to the insidious increase in CSF volume in idiopathic NPH are poorly understood, and the condition can likely occur from many different etiologies that influence CSF dynamics (ie, production or flow, or absorption) with a final common end point. The earliest theories regarding idiopathic NPH involved decreased CSF absorption leading to increased CSF volume over a protracted time frame, allowing for a compensatory increase in ventricular volume to maintain normal intracranial pressure. In support of these theories, a number of studies have shown a strong association between poor CSF absorption and good outcome after shunt surgery for idiopathic NPH. A study conducted by Boon and colleagues[10] showed that a higher resistance to outflow of CSF (known as R_{out}) was related to better surgical outcome.

Vascular Risk Factors

Animal models support that vascular mechanisms are related to the development of hydrocephalus. The spontaneously hypertensive rat model is known to produce hydrocephalus.[11] Pettorossi and colleagues[12] showed that increasing the pulse pressure with a balloon in the ventricle of the brain of sheep led to hydrocephalus in hours. Bering[13] showed that unilateral choroid plexectomy diminishes the amplitude of pressure pulsation in the one ventricle but not the mean pressure in both ventricles, and hydrocephalus was prevented in that ventricle. Human studies also support a role for vascular disease altering CSF dynamics and contributing to the development of NPH. Epidemiologic studies show that vascular risk factors are associated with NPH.[14,15] In the ARIC (Atherosclerosis Risk in Communities) study, pulse pressure and baseline systolic blood pressure were associated with enlargement of ventricles over 10 years.[16] As previously mentioned, Tisell and colleagues[6] completed a double-blind randomized study of 14 patients who had hydrocephalus, vascular risk factors, and, on testing, no CSF absorption problem, and patients improved with shunting.

EPIDEMIOLOGY

In a population-based study of 220,000 persons in Norway, the prevalence and incidence of NPH were 21.9 per 100,000 and 5.5 per 100,000, respectively.[17] In a large population-based sample using neuroimaging and clinical examinations, Jaraj and colleagues[18] found that the prevalence of probable NPH was 0.2% in persons 70 to 79 years of age and 5.9% in those older than 80 years of age. An estimate of ventricular enlargement (Evans index of >0.3) was present in 20.9%,

but an important imaging feature that is typically found in NPH that allows the ventriculomegaly of NPH to be distinguished from neurodegenerative causes of ventriculomegaly (occluded sulci at the high convexity) was only present in 5.4%.

Mori and colleagues[3] summarized three epidemiologic NPH studies in Japan. They reported the prevalence of idiopathic NPH with MRI support to be approximately 1.1% of persons older than 60 years of age.

The population-based Mayo Clinic Study of Aging found that among 1494 persons older than age 70 who had MRI scans, 20% had ventriculomegaly (an Evans index of 0.3 or greater) and 5% had ventriculomegaly and either a tight high convexity (occluded sulci at the high convexity) or extraventricular hydrocephalus (CSF fluid collection outside the ventricles not due to atrophy).[14]

WHY NORMAL PRESSURE HYDROCEPHALUS IS HARD TO DIAGNOSE AND MANAGE

One reason NPH is difficult to diagnose is that all the key "hallmark" findings are common in older persons and have many causes. Gait abnormality occurs in 20% of individuals older than age 75 and is associated with the development of dementia.[19] Incontinence occurs in 38% of women[20] and 18% of men[21] at this age. Fourteen percent of persons older than 70 years of age have dementia.[22] In 2017, the Alzheimer's Association reported that 5.5 million persons in the United State had Alzheimer dementia.[23] Ventricles enlarge with age[24] and with neurodegenerative dementias.[25] In the general population older than 70 years of age, 20% have ventriculomegaly (defined as an Evans index of >0.3).

Managing NPH is difficult because surgical complications with shunting are common. In a review of 30 studies conducted since 2006 that included 1573 patients, Toma and colleagues[26] summarized the complication rate of NPH surgery: mortality was 0.2%, subdural hemorrhage 4.5%, intracranial hemorrhage 0.2%, infection 3.5%, and revisions 13%.

To date, all diagnostic tests for NPH have both false-positive and false-negative results; these tests include absorption tests, monitoring CSF pressure, cisternography, flow in the cerebral aqueduct, high-volume lumbar puncture, and external CSF drainage.[2]

Patients with NPH commonly have overlapping comorbid diseases, including Alzheimer disease, Parkinson disease, parkinsonian syndromes, spinal stenosis, large joint disease, and neuropathy. For more information, refer to the authors' review of the comorbidities in NPH.[27]

CLINICAL FEATURES

The classic clinical presentation of NPH is that of an insidiously progressive gait syndrome, urinary urgency followed by incontinence, and cognitive impairment. This clinical triad is thought to occur because of impairment of periventricular frontal cortical–basal ganglia–thalamocortical circuitry in the setting of CSF hypervolemia.[28] In support of this, the authors have recently demonstrated that patients with idiopathic NPH show hypometabolism in the caudate nucleus,[29] and others have shown functional recovery of the supplementary motor area after CSF drainage.[30]

Gait Dysfunction

The gait dysfunction in NPH has traditionally been described as that of a "magnetic" or "glue-footed" gait, gait apraxia, or a frontal ataxia similar to what has been

KEY POINTS

- Factors associated with so-called idiopathic normal pressure hydrocephalus include impaired CSF absorption, vascular disease, and congenital hydrocephalus. All these factors may alter CSF dynamics in a way that can lead to increased CSF content in the cranial vault while maintaining a relatively normal average CSF pressure.
- Normal pressure hydrocephalus is an uncommon disease, but large ventricles are commonly seen in persons older than 70 years of age.
- No pathognomonic individual or combination of clinical features exists for normal pressure hydrocephalus. Comorbid diseases are common and should be evaluated.
- The triad of gait abnormality, incontinence, and cognitive impairment seen in normal pressure hydrocephalus may possibly be related to periventricular frontal cortical–basal ganglia–thalamocortical circuitry. Most often, patients with normal pressure hydrocephalus do not have the full triad of symptoms, and gait abnormality usually presents first.

described as Bruns ataxia. However, the gait abnormality can be highly variable and likely depends on the nature of the specific cortical–basal ganglia–thalamocortical circuitry disruption. The clinician considering a diagnosis of idiopathic NPH should focus on differentiating the gait observed from other potential causes of gait abnormalities in this clinical population (refer to the Approach to Diagnosis section). The diagnosis should not be excluded if a magnetic gait is not seen. Common features that are consistent with an idiopathic NPH-related gait abnormality include small steps, wide base, difficulty with turns (usually taking several steps to do so), and postural instability with a positive pull test.

Cognitive Impairment

The cognitive impairment in idiopathic NPH is usually described as frontosubcortical dementia,[31] but the exact quality and severity in any individual will depend on that individual's pattern of cortical–basal ganglia–thalamocortical circuitry disruption related to the distribution of increased CSF content in the cranial vault and any comorbid pathology. Some common cognitive features include psychomotor slowing, decreased attention and concentration, impaired executive functions, and apathy. Importantly, if an anomia is present,[32,33] a comorbid cortical neurodegenerative disease such as Alzheimer disease (AD) should be suspected.

Urinary Incontinence

The urinary symptoms of idiopathic NPH are consistent with the original clinical description of frontal lobe incontinence and include urgency, frequency, and,

TABLE 8-1 **Causes of Gait Abnormalities in the Differential Diagnosis of Normal Pressure Hydrocephalus**

Disease Entity	Common Causes and Comments
Spinal disease	Cervical and lumbar stenosis
Lower extremity large joint disease	Hip and knee arthritis
Peripheral neuropathy	Diabetic neuropathy
Visual impairment	Walking with bifocal lenses makes it hard to see the floor
Vestibular dysfunction	Peripheral vestibular dysfunction
Parkinson disease	The presence of a rest tremor, asymmetric signs/symptoms, or involvement of the face and arms should raise the suspicion of Parkinson disease
Parkinsonian syndromes	Lewy body disease, progressive supranuclear palsy, corticobasal degeneration, and multiple system atrophy
Medications	Phenothiazines and benzodiazepines
Alcohol abuse	Cerebellar degeneration, peripheral neuropathy
Cerebrovascular disease	Strokes and white matter changes
Cerebellar disease	Alcohol abuse, spinocerebellar degeneration
Postural hypotension	Blood pressure medications, alpha blockers for enlarged prostate, degenerative diseases (see parkinsonian syndromes above) associated with autonomic dysfunction

eventually, urgency incontinence.[34] The original localization of this syndrome included the anteromedial frontal lobe, the genu of the corpus callosum, and the anterior cingulate cortex. These regions are frequently impacted by increased CSF content in the ventricles and the subarachnoid space of the longitudinal fissure in idiopathic NPH. Urinary urgency is usually the first urinary sign of dysfunction, which then evolves into urge urinary incontinence. This symptom is typically compounded by a slow gait, making timely travel to the bathroom difficult. After a successful CSF diversion procedure, patients are frequently surprised and quite pleased with the degree of improvement in these urinary symptoms.

APPROACH TO DIAGNOSIS

Performing shunt surgery on patients with large ventricles and no gait abnormality has not been shown to be helpful. This was first noted by Miller Fisher[35] in 1978, and several other studies have confirmed it.[33,36] The approach should be to concentrate on patients with large ventricles and gait abnormality; to that end, clinicians should keep the differential diagnosis of gait abnormality in this age group in mind (TABLE 8-1). When taking the history and performing an examination, identifying prognostic features and common causes of gait dysfunction and incontinence can help in evaluating a patient for a shunt (TABLE 8-2[37–40]).

Diagnostic Tests

Many tests have been evaluated to predict which patients with ventriculomegaly will improve with shunt surgery. As discussed earlier in this article, the mechanisms that lead to NPH are many; therefore, identifying a single diagnostic test to predict shunt outcome has been challenging. Cisternography has not proven to be consistently helpful.[41] Absorption studies or resistance to outflow (R_{out}) may have false negatives,[42] although when abnormal, they are correlated with good outcome. CSF flow study through the aqueduct may have false positives,[43] and monitoring CSF pressure and quantifying B waves may have false negatives.[33,44] Some of these tests evaluate the pathogenesis of a subset of NPH, such as impaired absorption,[10] and result in false negatives.[10] Further, it has been shown that patients without absorption problems can improve with a shunt.[10]

In the authors' opinion, the most important tests are the MRI and tests that evaluate whether a shunt may improve symptoms, including an LP with high-volume CSF removal or external CSF drainage. The latter tests are not specific to the pathogenesis but evaluate whether a shunt will improve symptoms.

MAGNETIC RESONANCE IMAGING. The routine evaluation of the NPH clinical syndrome always begins with neuroimaging. High-resolution structural MRI with orthogonal reconstructions can allow for a more thorough examination of the relevant anatomic effects of hydrocephalus. The first step is usually establishing the presence of ventriculomegaly. This can quickly be quantified by measuring the Evans index (FIGURE 8-2), which is the ratio of the largest width of the frontal horns and the widest measure of the inner table of the skull at that level. When this ratio is greater than 0.3, the ventricles are considered to be enlarged.[2] One weakness in measuring the Evans index is that it correlates poorly with ventricular volume because the measurement is one-dimensional and dependent on the level at which the index is measured[45] (this issue is especially problematic for measures of the callosal angle). The Mayo Clinic Study of Aging found that quantitative volume ratios between the

KEY POINTS

- Cognitive features of normal pressure hydrocephalus include psychomotor slowing, decreased attention and concentration, impaired executive functions, and apathy. Anomia suggests the presence of a cortical dementia and is a poor prognostic factor when deciding about shunt placement.
- The differential diagnosis of gait abnormalities in the elderly is broad and should be reviewed in detail when evaluating patients for normal pressure hydrocephalus.
- A focused history and examination should be performed looking for diseases that can co-occur or mimic the symptoms of normal pressure hydrocephalus and looking for factors that may influence management.

frontal horns of the lateral ventricles divided by the total intracranial volume correlate better than the Evans index with measures of gait speed and cognition both cross-sectionally and longitudinally.[14] Nonetheless, the Evans index is easy to measure in the office and readily available to all.

In a true communicating hydrocephalus syndrome, CSF has the potential to increase volume not only in the ventricular system but also in the communicating subarachnoid space. In such cases, the CSF tends to collect in the major fissures in the brain and displace the surrounding brain tissue, leading to a compressed appearance of adjacent sulci. A characteristic pattern known as

TABLE 8-2 **Pertinent Features in History and Examination for Normal Pressure Hydrocephalus**

Feature	Why Feature Should Be Addressed
History	
Was gait difficulty onset before, at same time as, or after cognitive decline?	Gait onset before or at same time as cognitive difficulty is associated with a good prognosis with shunting; dementia preceding the gait difficulty is associated with a poor prognosis with shunting[35,37]
How long has the patient had cognitive difficulty?	Two or more years of cognitive decline before presentation indicates poor prognosis with shunting[33,38]
Does the patient have urinary difficulty? If so, what type and for how long?	Urinary urgency is the most common problem; incontinence is not necessary for the diagnosis
Has the patient fallen?	Stronger indication to intervene
Was the patient assessed for vascular risk factors?	Risk factors are associated with normal pressure hydrocephalus[15]
Does the patient have a history of alcohol abuse?	Poor prognosis from shunt point of view[32]
Does patient have a history of secondary causes, such as head injury, meningitis, brain surgery, previous brain hemorrhage?	Good prognosis from shunt point of view
Is the patient on an anticoagulant?	Important if considering lumbar puncture or surgery
Does the patient have sleep apnea?	Valsalva at night theoretically may aggravate hydrocephalus[39]
Is the patient in heart failure?	May raise CSF pressure
Does the patient have any spinal diseases?	Important contributor to gait dysfunction
Does the patient have any major arthritis?	Important contributor to gait dysfunction
Does the patient have diabetes mellitus?	Associated with peripheral neuropathy
Does the patient have any visual problems?	May affect gait
Does the patient have any auditory or vestibular difficulty?	May affect gait
Does the patient have any family history of neurologic disease?	Could be related to ataxia
Is the patient taking medications that affect gait or lower blood pressure?	Examples are phenothiazines, benzodiazepines, antihypertensives, and alpha blockers for prostate hypertrophy

CONTINUED ON PAGE 173

disproportionately enlarged subarachnoid space hydrocephalus (DESH) was first defined in 2010.[46] DESH includes a tight high convexity and enlarged sylvian fissures with ventriculomegaly (FIGURE 8-3). DESH is associated with a good response to shunting and is now included in in the Japanese guideline for management of NPH.[3] The ventriculomegaly combined with sylvian fissure expansion leads to displacement of the CSF from sulci at the convexity and medial portion of the brain, leading to the so-called tight appearance. Tightness at the high convexity has been shown to be predictive of a shunt-responsive NPH clinical syndrome.[47] When fluid in the sylvian fissure

CONTINUED FROM PAGE 172

Feature	Why Feature Should Be Addressed
Examination	
Measure head size	10% or more of patients with normal pressure hydrocephalus have a head size larger than the 98th percentile[8,9] (57.5 cm for women and 59 cm for men)
Measure postural blood pressure	Look for orthostatic hypotension
Evaluate reflexes for radiculopathy, signs of stroke, and myelopathy	Brain, spinal cord, nerve root, and peripheral nerve diseases affect gait
Check vision	May affect gait
Test hearing and vestibular function	May affect gait
Evaluate for peripheral neuropathy	May affect gait
Examine for parkinsonism	May affect gait
Check for ataxia	May affect gait
Check for arthritis	May affect gait
Measure body mass index	This correlates with elevated opening pressure[40]

CSF = cerebrospinal fluid.

FIGURE 8-2
Evans index. The Evans index is the maximal ventricular width in the frontal horns divided by the largest distance between the inner tables of the skull measured at the same level. When the Evans index is greater than 0.3, the ventricles are in the top 20% in size of persons older than 70 years of age.

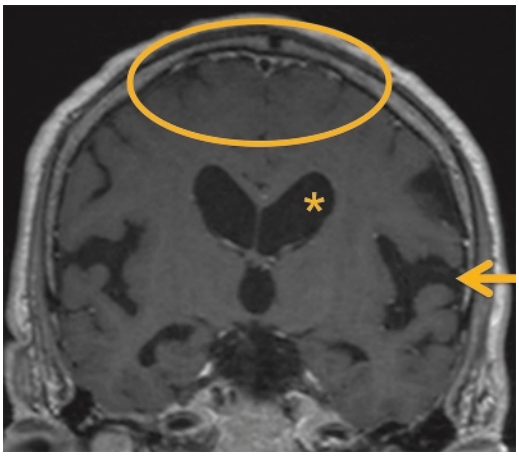

FIGURE 8-3
Disproportionately enlarged subarachnoid space hydrocephalus (DESH). Coronal T1-weighted MRI sequence with the three features characteristic of DESH highlighted. Ventriculomegaly (*asterisk*), increased CSF volume in the sylvian fissure (*arrow*), and the tight high convexity (*oval*). This finding has been incorporated into the Japanese guidelines for management of normal pressure hydrocephalus.

accumulates in connected sulci, the brain takes on an unusual anatomic appearance, especially when viewed on axial slices (FIGURE 8-4). This subarachnoid space expansion is frequently mistaken for atrophy or an arachnoid cyst, complicating the evaluation of patients with NPH. It is thus important for clinicians to become familiar with the anatomic patterns of fluid collection within the major brain fissures. Fluid tends to accumulate not only in the sylvian fissure but also in other major fissures (eg, calcarine, parietooccipital, and longitudinal fissures) and connected sulci (FIGURE 8-5). The authors have found that this imaging appearance can complicate NPH evaluation when it is mistaken for atrophy and the concomitant ventriculomegaly is interpreted as being *ex vacuo* (CASE 8-1).

In addition to high-resolution structural MRI for evaluation of anatomic patterns, axial FLAIR MRI is useful for evaluating for evidence of transependymal flow (FIGURE 8-6A) in addition to coexisting vascular pathology. The authors have also found it useful to include sagittal MRI sequences that have high signal from CSF to evaluate for partial obstruction (eg, fast imaging employing steady state acquisition C [FIESTA-C] or constructive interference in steady state [CISS] sequences, FIGURE 8-1).

HIGH-VOLUME LUMBAR PUNCTURE TEST. The exact way to perform a high-volume LP test for the evaluation of NPH is a matter of controversy. Differences among studies include using different

measures for outcome, measuring the outcomes at different times after the LP, and taking off different amounts of CSF. A meta-analysis looked at the eight "best" studies.[49] Patients were evaluated at different times after the LP, from 2 hours to 1 to 2 days later. The timing of when the patient is reevaluated for improvement after the high-volume LP is important because CSF is made at a rate of 0.3 mL/min; therefore, after 3 hours, the CSF withdrawn has been replaced. Yet, anecdotally, some patients report improvement 24 hours after the high-volume LP test. Several studies have used the LP as an indication for surgery, so the sensitivity could not be calculated. The meta-analysis concluded that if the high-volume LP test shows improvement in gait, the patient has an excellent chance of improving with shunt surgery.

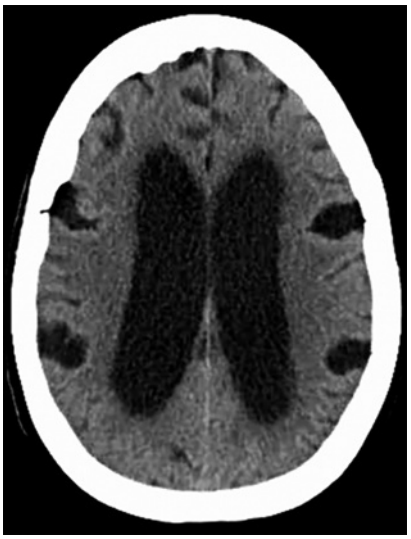

FIGURE 8-4
Characteristic finding of fluid collection in the anterior and posterior aspects of the sylvian fissure in normal pressure hydrocephalus. Axial head CT shows fluid pockets surrounded by tight sulci. This characteristic finding in normal pressure hydrocephalus is sometimes mistaken for atrophy or arachnoid cysts when viewed on only one of the three anatomic planes.

The authors perform the high-volume LP test by videotaping the patient's gait before the LP. After removing 30 mL CSF with the LP, the patient's gait is again videotaped within 30 minutes. Three measures of the gait are documented: (1) the time taken to walk 10 meters, turn 180 degrees, and return to the starting point; (2) the number of steps needed to turn 180 degrees twice, averaged; (3) the number of steps needed to turn 360 degrees 3 times, averaged. Improvement on any one of these measures is regarded as gait improvement (**VIDEO 8-1**, *links.lww.com/CONT/A268*). It has been shown that some patients who did not improve with a high-volume LP test may still improve with shunt surgery, suggesting that high-volume LP tests may result in false negatives.[50] This study[50] should be interpreted cautiously because patients were evaluated 6 to 8 hours after the LP. Nonetheless, the authors advise patients that if the LP test is negative, a subset of patients who have the clinical and imaging features of NPH may still have a chance of improving with a shunt, but this is much less likely than if the LP test was positive.

EXTERNAL LUMBAR DRAINAGE. For an external lumbar drain, patients are admitted to the hospital for placement of the drain. One method is to remove 10 mL CSF per hour. This study can be done for 1 to 3 days. The patient is evaluated for improvement in gait, cognition, or both. Despite the more invasive nature of an external lumbar drain, false negatives still occur,[50] similar to the LP test. Meningitis is an important complication with an external lumbar drain, and in a large series, 3.6% of patients developed an infection.[51] Placement of an external lumbar drain is most often undertaken in experienced centers and is considered in patients who have a negative LP test and when the patient, family, and doctors are struggling with the decision to decide on surgery.

KEY POINTS

- **In the assessment of patients for NPH, establish that there is ventriculomegaly; look for congenital factors such as aqueductal stenosis or webbing; and recognize the features of disproportionately enlarged subarachnoid space hydrocephalus (DESH), not mistaking DESH for atrophy.**
- **The two best diagnostic tests for normal pressure hydrocephalus are evaluating the MRI for the characteristic features, and performance of a high-volume lumbar puncture, measuring gait features objectively before and within 30 minutes after the lumbar puncture.**

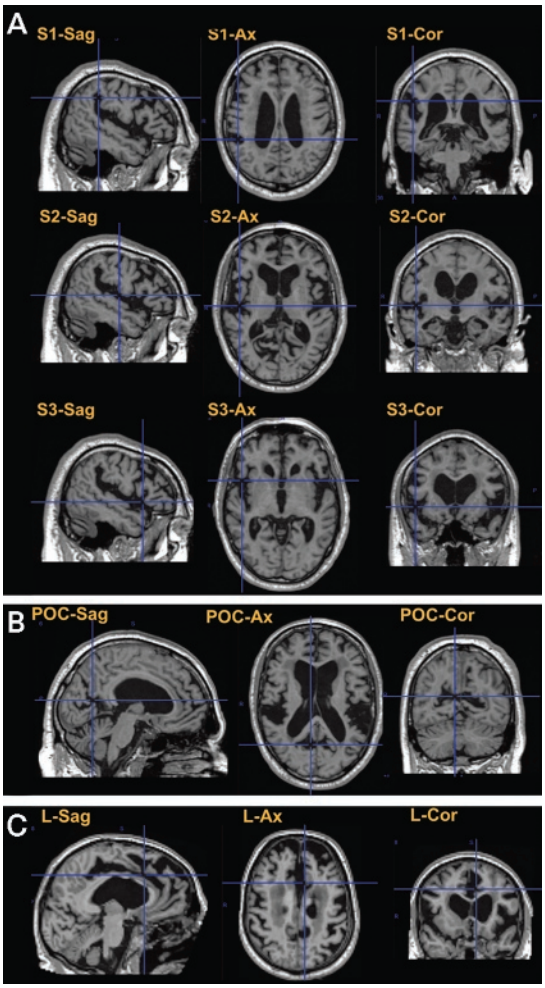

FIGURE 8-5

Anatomic patterns of subarachnoid hydrocephalus within major brain fissures and connected sulci. The anatomic patterns of subarachnoid hydrocephalus are best appreciated on yoked orthogonal MRI sections (sagittal, coronal, and axial views centered on the same point in the image). *A,* MRI of a patient with prominent subarachnoid hydrocephalus in the bilateral sylvian fissures and connected sulci is displayed using three orthogonal sections highlighting the posterior aspect of the fissure (*S1*), the middle portion of the fissure (*S2*), and the anterior portion of the fissure (*S3*). *B,* The same patient also had prominent subarachnoid hydrocephalus in the parietooccipital (POC) and calcarine fissures. The CSF volume in these fissures dramatically reduced after a ventriculoperitoneal shunting procedure (not shown). *C,* MRI of a different patient demonstrates anatomic patterns that can be observed with subarachnoid hydrocephalus involving the longitudinal fissure and connected sulci, such as the cingulate sulcus. Note the tight sulci seen on the midsagittal slice above the calcarine fissure (*L-Sag*) and the tight sulci on the upper cuts on the posterior portion of the axial slices (*L-Ax*).

OVERLAPPING DISEASES

The average age of patients who receive shunts for NPH is approximately 75, when many of the comorbid diseases discussed become common.[36] Thus, it is not surprising that persons being considered for shunt surgery may have several diseases that can complicate diagnosis.[27] Considering whether coexisting AD is present is important. In an autopsy series of persons without dementia, Braak and Braak[52] noted that at 71 to 75 years of age, 26% of patients had stage B and stage C amyloid pathology and 21% had stage III to stage VI tau pathology. At 76 to 80 years of age, 40% had stage B and stage C amyloid pathology and 37% had stage III to stage VI tau pathology. In four studies in which the brain was biopsied at the time of the shunt placement for NPH, about 30% of patients had AD pathology by biopsy,[53–56] consistent with the expected percentage based on age from the Braak and Braak study. Therefore, it should be suspected that about 30% of persons shunted have coexisting AD pathology.

While AD pathology is an important comorbid disease confounding the cognitive features of NPH, Parkinson disease and other neurodegenerative parkinsonian syndromes causing gait abnormality are important conditions to consider when evaluating the motor aspects of NPH.[57] Dopamine transporter single-photon emission computed

tomography (SPECT) scanning[58] and iodine-123 metaiodobenzylguanidine [MIBG] SPECT scanning of the heart[59] have been proposed as biomarkers of neurodegenerative parkinsonian syndromes that may predict a poor response to shunt. However, these modalities are limited in that they are only able to detect a subset of comorbid neurodegenerative conditions and do not have positive findings suggestive of the presence of NPH. FDG-PET may also serve as a useful diagnostic biomarker in evaluating a patient for NPH because, in addition to detecting an AD pattern of hypometabolism,[60] FDG-PET is abnormal in a wide range of neurodegenerative diseases. The presence of caudate hypometabolism has been identified as a potential biomarker in NPH.[29] In addition to evaluating for the presence of comorbid neurodegenerative diseases with FDG-PET, normal cortical metabolism will rule out most neurodegenerative sources of *ex vacuo* ventriculomegaly and limit misinterpretation of subarachnoid hydrocephalus (FIGURE 8-6).

Spinal diseases, arthritis, peripheral neuropathy, cerebellar diseases, and orthostatic hypotension are crucial to recognize when evaluating a patient for NPH.[27]

CEREBROSPINAL FLUID BIOMARKERS

CSF measures of AD proteins were considered potential biomarkers to readily distinguish patients with AD from patients with NPH. In AD, amyloid-β_{1-42} is low in the CSF, while total tau (t-tau) and phosphorylated tau (p-tau) are elevated. In patients with NPH, however, many proteins, including metabolites of amyloid precursor protein (APP) (eg, amyloid-β_{1-40}, amyloid-β_{1-42}, soluble amyloid precursor protein α [sAPPα], and soluble amyloid precursor protein β [sAPPβ]), t-tau, and p-tau are low, and these normalize after a shunt is placed.[61] The finding of low amyloid-β_{1-42} and low tau in NPH has been confirmed in several studies.[62,63] The exact reason these proteins are low in NPH is unknown, but studies have shown that during sleep the nerve cells shrink and the interstitial space increases, facilitating metabolic product drainage.[64] The authors[65] have hypothesized that in NPH, the typical drainage of metabolic products is impaired because the cells and interstitial space are tight, resulting in many proteins being low when measured in the CSF of patients with NPH, but these proteins return to normal after a shunt is placed.[61] Because amyloid-β_{1-42} is low in both NPH and AD, the utility of CSF biomarkers in distinguishing AD from NPH is limited. The presence of elevated t-tau or p-tau would be inconsistent with NPH and suggestive of a primary or at least coexisting neurodegenerative disease.

SURGICAL CONSIDERATIONS

Important surgical considerations in NPH include the use of adjustable shunts, the complications of surgery, and setting the valve opening pressure.

Adjustable Shunts Versus Fixed-Opening-Pressure Shunts

Over the past decades, adjustable shunts have slowly replaced fixed-pressure shunts. In the Swedish registry of patients with NPH who underwent shunt surgery between 2004 and 2015,[66] 10% developed subdural hematomas. Of these, 103 subdural hematomas were treated by adjusting the shunts, while 66 had surgical drainage and 15 had no treatment. Of those with fixed-pressure shunt valves, 90% were treated with surgery, but only 30% with adjustable valves were treated surgically. The study concluded that subdural hematomas are

KEY POINTS

- **Overlapping chronic diseases are common in persons being considered for shunt surgery because their average age is about 74 years. At this age, 30% of cognitively normal persons have Alzheimer disease pathology. Fludeoxyglucose positron emission tomography may help reveal a concomitant degenerative disease.**
- **In idiopathic normal pressure hydrocephalus, most metabolic proteins are low in the CSF, so Alzheimer biomarkers (eg, amyloid-β_{1-42} and phosphorylated tau) are also low and are not helpful in distinguishing Alzheimer disease from idiopathic normal pressure hydrocephalus.**

CASE 8-1

A 68-year-old woman presented with a 2-year history of progressive gait disturbance. She had used a walker for the past 4 months and had noticed difficulty with turning and imbalance but no freezing. She had no tremors, delusions, hallucinations, dream enactment, head trauma, or history of central nervous system infection but had memory difficulty. She had experienced urinary incontinence for 6 years, which worsened when treated with oxybutynin.

Lumbar spine MRI demonstrated mild to moderate canal stenosis at L3 through L5. MRI of the cervical spine demonstrated moderately severe bilateral neural foraminal stenosis at C4 to C5. Brain MRI demonstrated hydrocephalus with high periventricular fluid-attenuated inversion recovery (FLAIR) signal suggestive of normal pressure hydrocephalus. CSF collections outside of the ventricle were seen as well (FIGURE 8-6A). The patient had undergone a high-volume lumbar puncture by a previous neurologist and reported improvement in her symptoms; however, the diagnosis was questioned, and she sought a second opinion.

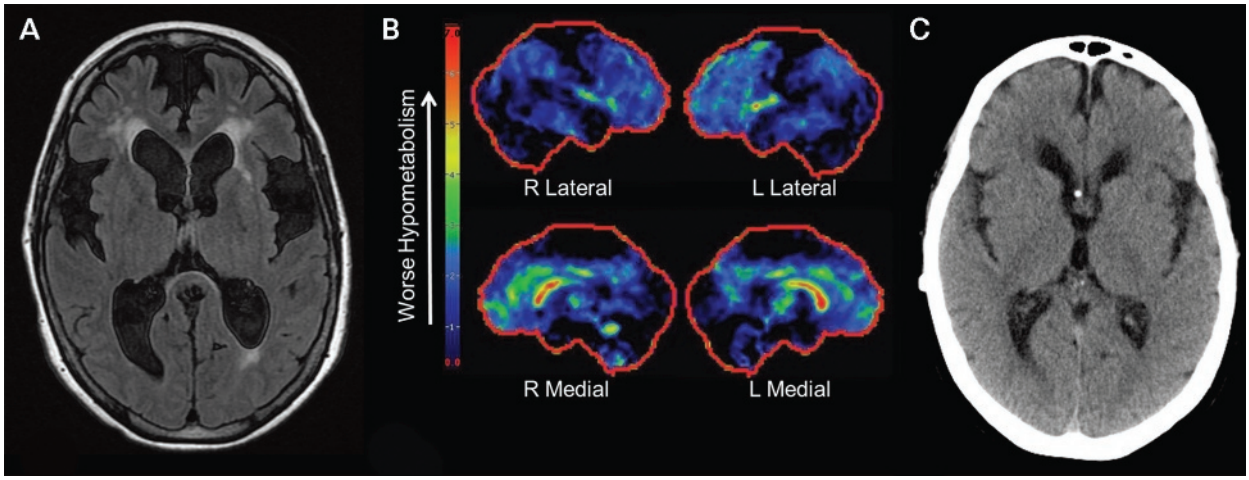

FIGURE 8-6

Ventricular, sylvian fissure, and longitudinal fissure hydrocephalus in the absence of neurodegenerative hypometabolism in the patient in CASE 8-1. *A,* Baseline axial fluid-attenuated inversion recovery (FLAIR) MRI sequence demonstrates ventriculomegaly with subarachnoid hydrocephalus in the sylvian and longitudinal fissures. Periventricular high T2 signal is also present. *B,* Baseline fludeoxyglucose positron emission tomography (FDG-PET) demonstrating normal cortical metabolism in the brain tissue around the sylvian and longitudinal fissures with subtle artifactual hypometabolism seen in these same areas (*green-colored regions*) related to partial volume averaging. There is a notable absence of a neurodegenerative pattern of hypometabolism. True hypometabolism is seen in the striatum, which commonly occurs in normal pressure hydrocephalus. *C,* Axial CT scan demonstrating resolution of the ventricular, sylvian fissure, and longitudinal fissure hydrocephalus 17 months after a ventriculoperitoneal shunt was placed.

On examination, she scored 29/38 on the Kokmen Short Test of Mental Status (orientation 6/8, digit span 5/7, learning 4/4 with two trials, calculation 3/4, abstraction 3/3, construction 4/4, information 4/4, recall 2/4). (The normal score on the Kokmen Short Test of Mental Status is 34.2 +/− 2.4.[48]) Speech and language were normal. Her neurologic examination was normal with the exception of having a wide base while standing, difficulty moving while sitting on the examination table, and walking slowly with a wide base. She took nine steps to turn 180 degrees. She did not freeze while walking.

Her neuropsychological testing demonstrated prominent cognitive slowing along with mild to moderate deficits in aspects of executive function, learning, and memory. The patient needed assistance with activities of daily living, so the findings were in keeping with a mild dementia.

A high-volume lumbar puncture (30 mL) was performed and demonstrated significant improvement in her walking speed and turns. The opening pressure was 232 mm H_2O, and the CSF cell count, protein, and glucose were normal. Fludeoxyglucose positron emission tomography (FDG-PET) demonstrated normal cortical metabolism, providing evidence against a neurodegenerative etiology (FIGURE 8-6B).

She underwent ventriculoperitoneal shunt placement. On her return visit 17 months after surgery, her CT scan showed improvement in ventricular size and fluid in the sylvian and longitudinal fissures (FIGURE 8-6C). Clinically, her cognition also improved (she scored 35/38 on the Kokmen Short Test of Mental Status). Her gait was normal, and her urinary incontinence had resolved.

COMMENT

This case illustrates the major clinical features of normal pressure hydrocephalus. The patient's main problem was gait difficulty, but she also had clear cognitive and urinary problems, which all resolved with shunting. The fluid collections outside of the ventricles made the diagnosis difficult, with some suspicion that the fluid collections were due to atrophy. FDG-PET was helpful because it showed no cortical hypometabolism, supporting that a concomitant degenerative disease was unlikely. Her follow-up scan showed improvement in the fluid collections outside of the ventricles, indicating that this was part of the hydrocephalus and confirming the fluid collections were not secondary to atrophy.

common after shunt surgery, but adjustable shunts decrease the need for surgical intervention. TABLE 8-3 reports the declining complication rate of shunt placement by decade.

Setting the Opening Valve Pressure

When the opening valve pressure is set to a level much lower than the opening LP CSF pressure, a greater chance of overdrainage complications exists, such as subdural hematoma, subdural hygroma, or headache.[40] The patient's body mass index has been associated with the LP opening pressure, with patients who are overweight having higher LP opening pressures. The authors' practice has changed to now set the valve opening pressure at the LP opening pressure to try to decrease overdrainage. The authors recommend that each center review its own complication rate so that specific advice can be given when advising a patient and family regarding complications of shunt surgery.

How to Evaluate Improvement

The authors recommend both the mRS and the Normal Pressure Hydrocephalus Scale for detailed evaluation of improvement in NPH.

MODIFIED RANKIN SCALE. The mRS has been used in NPH and stroke studies.[5] It is a subjective assessment of change but has a track record in important clinical trials; it measures patient functionality, which is crucial in judging shunt benefit. Use of this scale allows comparison of patients and their outcomes to those in other NPH studies that used the scale. Reliability is improved with a structured interview.[67]

NORMAL PRESSURE HYDROCEPHALUS SCALE. A standardized Normal Pressure Hydrocephalus Scale[68] was used in the European Multicenter NPH study to quantitatively measure the cardinal clinical features of NPH. It is a 0- to 100-point scale that measures the key features of NPH: gait, cognition, balance, and urine control. All items are weighted equally except gait, which contributes double weight compared to the other components. Hellström and colleagues[68] give the details of how to combine the individual measures to obtain an overall 0 to 100 score.

TABLE 8-3 **Complication Rate in Normal Pressure Hydrocephalus by Decade**[a]

Decade	Number of Studies	Number of Patients	Mortality (%)	Subdural Hematoma (%)	Intracranial Hemorrhage (%)	Infection (%)	Seizures (%)	Revision Rate (%)
1970s	2	92	9.5	4.1	0	8.2	1.3	17.8
1980s	8	262	5	15	1.3	1.7	4.8	14
1990s	12	459	3.2	14	0	2	0.7	27
2000s	42	2250	0.3	4.8	0.4	3.6	0	19
2006 to October 2010	30	1573	0.2	4.5	0.2	3.5	0	13

[a] Reprinted with permission from Toma AK, et al, Acta Neurochir (Wien).[26] © 2013 Springer-Verlag Wien.

GAIT SCALE. The gait scale consists of three measures:

- **A timed walk for 10 meters (free pace)**
- **The number of steps the patient took to make this walk**
- **An ordinal scale from 1 to 8 for walking (TABLE 8-4)**

COGNITIVE SCALE. The cognitive scale consists of three tests that contribute four cognitive variables. The grooved pegboard test evaluates speed of manual dexterity. The patient must place 25 pegs into holes with randomly positioned slots as quickly as possible. The task is performed once with each hand, beginning with the dominant hand. Time to completion for the faster hand is used to determine the test score. The Rey Auditory Verbal Learning Test is a 15-word list-learning test. The words are read aloud by the examiner at a rate of approximately one word per second; immediately afterward, the patient is asked to recall as many words as possible from the list. The same list is read five consecutive times, and the sum of words recalled correctly across all trials contributes to the overall cognitive score. The Swedish Stroop test is a task that measures processing speed and complex attention/executive function. Two tasks are administered: a color-naming task and an interference task. In the color-naming task, the patient is asked to name the colors of 100 rectangles presented in a 10 by 10 matrix as quickly as possible. In the interference task, the patient is asked to name, again as quickly as possible, the color of the ink of 100 incongruently colored color words (eg, the word *green* printed in yellow).

BALANCE SCALE. The balance scale consists of an ordinal scale converted to 100 points based on observations of the patient's efforts to stand up straight on one or both legs. An ordinal rating is given (TABLE 8-5).

CONTINENCE SCALE. The continence scale is also an ordinal scale (TABLE 8-6). The rating is based on information of the most trustworthy source available, as patients with reduced insight may deny incontinence despite its presence.

OTHER ASSESSMENTS FOR IMPROVEMENT. From a clinical point of view, physicians could also use a combination of videotaping the patient's gait (eg, walking 10

Gait Scale of Normal Pressure Hydrocephalus Scale[a] TABLE 8-4

1 Normal
2 Slight disturbance of tandem walk and turning
3 Wide-based gait with sway, without foot corrections
4 Tendency to fall, with foot corrections
5 Walking with cane
6 Bimanual support needed
7 Aided
8 Wheelchair dependent

[a] Reprinted with permission from Hellström P, et al, Acta Neurol Scand.[68] © 2012 John Wiley & Sons.

TABLE 8-5

Balance Scale of Normal Pressure Hydrocephalus Scale[a]

1 Able to stand independently for 30 seconds or more on either lower extremity alone

2 Able to stand independently for less than 30 seconds on either lower extremity alone

3 Able to stand independently with the feet together (at the heels) for more than 30 seconds or more

4 Able to stand independently with the feet together for less than 30 seconds

5 Able to stand independently with the feet 1 foot apart for 30 seconds or more

6 Able to stand independently with the feet 1 foot apart for less than 30 seconds

7 Unable to stand without assistance

[a] Reprinted with permission from Hellström P, et al, Acta Neurol Scand.[68] © 2012 John Wiley & Sons.

TABLE 8-6

Incontinence Scale of Normal Pressure Hydrocephalus Scale[a]

1 Normal urinary function

2 Urgency without incontinence

3 Infrequent incontinence without a diaper

4 Frequent incontinence with a diaper

5 Bladder incontinence

6 Bladder and bowel incontinence

[a] Reprinted with permission from Hellström P, et al, Acta Neurol Scand.[68] © 2012 John Wiley & Sons.

TABLE 8-7

Long-term Outcome of Shunt Surgery by Decade[a]

Decade	Studies (N)	Patients (N)	Age (Mean)	Improved at 3 Months (%)	Improved at 1 Year (%)	Improved at More Than 3 Years (%)
1970s	2	92	67	67.5	45	No data available
1980s	8	262	67	68	53	No data available
1990s	12	459	68	64	81	40
2000s	42	2250	70	74	79	72
2006 to October 2010	30	1573	71	81	82	73

[a] Reprinted with permission from Toma, AK, et al, Acta Neurochir.[26] © 2013 Springer-Verlag.

meters, turning 180 degrees, and returning) and a standardized short test such as the Kokmen Short Test of Mental Status,[69] Mini-Mental State Examination (MMSE),[70] or the Montreal Cognitive Assessment (MoCA).[71]

Prognosis After Shunting

Determining the long-term outcomes after shunt surgery is a controversial area. One meta-analysis shows that surgical prognosis has improved over time (TABLE 8-7). Others have pointed out that in an intention-to-treat analysis, the number of individuals improving would be lower.[72]

When the authors discuss the high complication risk and the long-term outcome for shunt surgery with patients and their families, patients most frequently still choose to undergo the procedure and take the risk because the alternatives are so bleak. A patient with difficulty walking and incontinence has a large chance of being cared for in a nursing home. Further, the patients' risk of falling increases their risk of hospitalization.

KEY POINTS

- **Surgical complications following shunt surgery are common but have decreased over the decades. Adjustable shunts allow treatment of overdrainage without surgical intervention.**
- **Objective measurements to assess patient change with shunt placement are very helpful in management.**
- **Surgical outcome is improving, and patients who are seen in follow-up 3 years after shunt surgery have a good chance of remaining improved.**

CONCLUSION

NPH is a rare, but treatable, disease. The diagnosis can be difficult because many diseases can cause cognitive impairment, incontinence, and gait dysfunction. Treating well-selected patients can result in clinical improvement, but the risks and benefits of the shunt procedure must be weighed. Recent improvements in understanding the neuroimaging features of NPH have allowed improved identification and selection of patients with NPH. In the future, a randomized double-blind clinical trial is needed to evaluate the short- and long-term clinical outcome and complication rate for NPH. Since shunts now have a virtual "off" setting, this could potentially be completed with half the shunted patients having the shunt set at "off" for a period and half having the shunt set at "on" immediately.[7]

VIDEO LEGEND

VIDEO 8-1
Gait in normal pressure hydrocephalus before and after high-volume lumbar puncture test and after ventriculoperitoneal shunt surgery. A 64-year-old woman with normal pressure hydrocephalus. Video on the left demonstrates the baseline gait of the patient. Video on the right shows her gait 30 minutes after removing 30 mL CSF and her gait 6 months after shunting.
links.lww.com/CONT/A268

REFERENCES

1 Adams RD, Fisher CM, Hakim S, et al. Symptomatic occult hydrocephalus with "normal" cerebrospinal-fluid pressure. A treatable syndrome. N Engl J Med 1965;273:117–126. doi:10.1056/NEJM196507152730301.

2 Relkin N, Marmarou A, Klinge P, et al. Diagnosing idiopathic normal-pressure hydrocephalus. Neurosurgery 2005;57(3 suppl):S4–S16; discussion ii–v. doi:10.1227/01.NEU.0000168185.29659.C5.

3 Mori E, Ishikawa M, Kato T, et al. Guidelines for management of idiopathic normal pressure hydrocephalus: second edition. Neurol Med Chir (Tokyo) 2012;52(11):775–809. doi:10.2176/nmc.52.775.

4 Halperin JJ, Kurlan R, Schwalb JM, et al. Practice guideline: idiopathic normal pressure hydrocephalus: response to shunting and predictors of response: report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology. Neurology 2015;85(23):2063–2071. doi:10.1212/WNL.0000000000002193.

5 Kazui H, Miyajima M, Mori E, et al. Lumboperitoneal shunt surgery for idiopathic normal pressure hydrocephalus (SINPHONI-2): an open-label randomised trial. Lancet Neurol 2015;14(6):585–594. doi:10.1016/S1474-4422(15)00046-0.

6 Tisell M, Tullberg M, Hellström P, et al. Shunt surgery in patients with hydrocephalus and white matter changes. J Neurosurg 2011;114(5):1432–1438. doi:10.3171/2010.11.JNS10967.

7 Saper CB. The emperor has no clothes. Ann Neurol 2016;79(2):165–166. doi:10.1002/ana.24603.

8 Krefft TA, Graff-Radford NR, Lucas JA, Mortimer JA. Normal pressure hydrocephalus and large head size. Alzheimer Dis Assoc Disord 2004;18(1):35–37.

9 Wilson RK, Williams MA. Evidence that congenital hydrocephalus is a precursor to idiopathic normal pressure hydrocephalus in only a subset of patients. J Neurol Neurosurg Psychiatry 2007;78(5):508–511. doi:10.1136/jnnp.2006.108761.

10 Boon AJ, Tans JT, Delwel EJ, et al. Dutch normal-pressure hydrocephalus study: prediction of outcome after shunting by resistance to outflow of cerebrospinal fluid. J Neurosurg 1997;87(5):687–693. doi:10.3171/jns.1997.87.5.0687.

11 Ritter S, Dinh TT. Progressive postnatal dilation of brain ventricles in spontaneously hypertensive rats. Brain Res 1986;370(2):327–332. doi:10.1016/0006-8993(86)90488-9.

12 Pettorossi VE, Di Rocco C, Mancinelli R, et al. Communicating hydrocephalus induced by mechanically increased amplitude of the intraventricular cerebrospinal fluid pulse pressure: rationale and method. Exp Neurol 1978;59(1):30–39. doi:10.1016/0014-4886(78)90198-X.

13 Bering EA Jr. Circulation of the cerebrospinal fluid. Demonstration of the choroid plexuses as the generator of the force for flow of fluid and ventricular enlargement. J Neurosurg 1962;19:405–413. doi:10.3171/jns.1962.19.5.0405.

14 Graff-Radford N, Gunter J, Thomas C, et al. Ventriculomegaly is a biomarker of gait and cognitive decline. Alzheimers Dement 2017;13(7 suppl):1092. doi:10.1016/j.jalz.2017.06.1572.

15 Jaraj D, Agerskov S, Rabiei K, et al. Vascular factors in suspected normal pressure hydrocephalus: a population-based study. Neurology 2016;86(7):592–599. doi:10.1212/WNL.0000000000002369.

16 Graff-Radford NR, Knopman DS, Penman AD, et al. Do systolic BP and pulse pressure relate to ventricular enlargement? Eur J Neurol 2013;20(4):720–724. doi:10.1111/ene.12067.

17 Brean A, Eide PK. Prevalence of probable idiopathic normal pressure hydrocephalus in a Norwegian population. Acta Neurol Scand 2008;118(1):48–53. doi:10.1111/j.1600-0404.2007.00982.x.

18 Jaraj D, Rabiei K, Marlow T, et al. Prevalence of idiopathic normal-pressure hydrocephalus. Neurology 2014;82(16):1449–1454. doi:10.1212/WNL.0000000000000342.

19 Verghese J, Lipton RB, Hall CB, et al. Abnormality of gait as a predictor of non-Alzheimer's dementia. N Engl J Med 2002;347(22):1761–1768. doi:10.1056/NEJMoa020441.

20 Anger JT, Saigal CS, Litwin MS; Urologic Diseases of America Project. The prevalence of urinary incontinence among community dwelling adult women: results from the National Health and Nutrition Examination Survey. J Urol 2006;175(2):601–604. doi:10.1016/S0022-5347(05)00242-9.

21 Stothers L, Thom D, Calhoun E. Urologic diseases in America project: urinary incontinence in males-demographics and economic burden. J Urol 2005;173(4):1302–1308. doi:10.1097/01.ju.0000155503.12545.4e.

22 Plassman BL, Langa KM, Fisher GG, et al. Prevalence of dementia in the United States: the aging, demographics, and memory study. Neuroepidemiology 2007;29(1–2):125–132. doi:10.1159/000109998.

23 Hebert LE, Weuve J, Scherr PA, Evans DA. Alzheimer disease in the United States (2010-2050) estimated using the 2010 census. Neurology 2013;80(19):1778–1783. doi:10.1212/WNL.0b013e31828726f5.

24 Barron SA, Jacobs L, Kinkel WR. Changes in size of normal lateral ventricles during aging determined by computerized tomography. Neurology 1976;26(11):1011–1013. doi:10.1212/WNL.26.11.1011.

25 Jack CR Jr, Shiung MM, Gunter JL, et al. Comparison of different MRI brain atrophy rate measures with clinical disease progression in AD. Neurology 2004;62(4):591–600. doi:10.1212/01.WNL.0000110315.26026.EF.

26 Toma AK, Papadopoulos MC, Stapleton S, et al. Systematic review of the outcome of shunt surgery in idiopathic normal-pressure hydrocephalus. Acta Neurochir (Wien) 2013;155(10):1977–1980. doi:10.1007/s00701-013-1835-5.

27 Malm J, Graff-Radford NR, Ishikawa M, et al. Influence of comorbidities in idiopathic normal pressure hydrocephalus—research and clinical care. A report of the ISHCSF task force on comorbidities in INPH. Fluids Barriers CNS 2013;10(1):22. doi:10.1186/2045-8118-10-22.

28 Curran T, Lang AE. Parkinsonian syndromes associated with hydrocephalus: case reports, a review of the literature, and pathophysiological hypotheses. Mov Disord 1994;9(5):508–520. doi:10.1002/mds.870090503.

29 Townley RA, Botha H, Graff-Radford J, et al. 18F-FDG PET-CT pattern in idiopathic normal pressure hydrocephalus. Neuroimage Clin 2018; 18:897–902. doi:10.1016/j.nicl.2018.02.031.

30 Lenfeldt N, Larsson A, Nyberg L, et al. Idiopathic normal pressure hydrocephalus: increased supplementary motor activity accounts for improvement after CSF drainage. Brain 2008; 131(pt 11):2904–2912. doi:10.1093/brain/awn232.

31 Picascia M, Zangaglia R, Bernini S, et al. A review of cognitive impairment and differential diagnosis in idiopathic normal pressure hydrocephalus. Funct Neurol 2015;30(4):217–228. doi:10.11138/FNeur/2015.30.4.217.

32 De Mol J. Prognostic factors for therapeutic outcome in normal-pressure hydrocephalus. Review of the literature and personal study [in French]. Acta Neurol Belg 1985;85(1):13–29.

33 Graff-Radford NR, Godersky JC, Jones MP. Variables predicting surgical outcome in symptomatic hydrocephalus in the elderly. Neurology 1989;39(12):1601–1604. doi:10.1212/WNL.39.12.1601.

34 Andrew J, Nathan PW. Lesions on the anterior frontal lobes and disturbances of micturition and defaecation. Brain 1964;87:233–262. doi:10.1093/brain/87.2.233.

35 Fisher CM. Communicating hydrocephalus. Lancet 1978;1(8054):37. doi:10.1016/S0140-6736(78)90378-1.

36 Marmarou A, Young HF, Aygok GA, et al. Diagnosis and management of idiopathic normal-pressure hydrocephalus: a prospective study in 151 patients. J Neurosurg 2005;102(6):987–997. doi:10.3171/jns.2005.102.6.0987.

37 Graff-Radford NR, Godersky JC. Normal-pressure hydrocephalus. Onset of gait abnormality before dementia predicts good surgical outcome. Arch Neurol 1986;43(9):940–942. 10.1001/archneur.1986.00520090068020.

38 Petersen RC, Mokri B, Laws ER Jr. Surgical treatment of idiopathic hydrocephalus in elderly patients. Neurology 1985;35(3):307–311. doi:10.1212/WNL.35.3.307.

39 Oliveira MF, Nacif SR, Castellano O, et al. Improvement of central sleep apneas following ventricular shunt for normal pressure hydrocephalus. J Neuropsychiatry Clin Neurosci 2015;27(3):e206–e208. doi:10.1176/appi.neuropsych.14120375.

40 Khan QU, Wharen RE, Grewal SS, et al. Overdrainage shunt complications in idiopathic normal-pressure hydrocephalus and lumbar puncture opening pressure. J Neurosurg 2013; 119(6):1498–1502. doi:10.3171/2013.7.JNS13484.

41 Vanneste J, Augustijn P, Dirven C, Tan WF, Goedhart ZD. Shunting normal-pressure hydrocephalus: do the benefits outweigh the risks? A multicenter study and literature review. Neurology 1992;42(1):54–59. doi:10.1212/WNL.42.1.54.

42 Boon AJ, Tans JT, Delwel EJ, et al. Dutch normal-pressure hydrocephalus study: the role of cerebrovascular disease. J Neurosurg 1999; 90(2):221–226. doi:10.3171/jns.1999.90.2.0221.

43 Dixon GR, Friedman JA, Luetmer PH, et al. Use of cerebrospinal fluid flow rates measured by phase-contrast MR to predict outcome of ventriculoperitoneal shunting for idiopathic normal-pressure hydrocephalus. Mayo Clin Proc 2002;77(6):509–514. doi:10.4065/77.6.509.

44 Børgesen SE, Gjerris F. The predictive value of conductance to outflow of CSF in normal pressure hydrocephalus. Brain 1982;105(pt 1): 65–86. doi:10.1093/brain/105.1.65.

45 Toma AK, Holl E, Kitchen ND, Watkins LD. Evans' index revisited: the need for an alternative in normal pressure hydrocephalus. Neurosurgery 2011;68(4):939–944. doi:10.1227/NEU.0b013e318208f5e0.

46 Hashimoto M, Ishikawa M, Mori E, et al. Diagnosis of idiopathic normal pressure hydrocephalus is supported by MRI-based scheme: a prospective cohort study. Cerebrospinal Fluid Res 2010;7:18. doi:10.1186/1743-8454-7-18.

47 Narita W, Nishio Y, Baba T, et al. High-convexity tightness predicts the shunt response in idiopathic normal pressure hydrocephalus. AJNR Am J Neuroradiol 2016;347(10):1831–1837. doi:10.3174/ajnr.A4838.

48 Tang-Wai DF, Knopman DS, Geda YE, et al. Comparison of the Short Test of Mental Status and the Mini-Mental State Examination in cognitive impairment. Arch Neurol 2003;60(12): 1777–1781. doi:10.1001/archneur.60.12.1777.

49 Mihalj M, Dolić K, Kolić K, Ledenko V. CSF tap test—obsolete or appropriate test for predicting shunt responsiveness? A systemic review. J Neurol Sci 2016;362:78–84. doi:10.1016/j.jns.2016.01.028.

50 Walchenbach R, Geiger E, Thomeer RT, Vanneste JA. The value of temporary external lumbar CSF drainage in predicting the outcome of shunting on normal pressure hydrocephalus. J Neurol Neurosurg Psychiatry 2002;72(4):503–506. doi:10.1136/jnnp.72.4.503.

51 Greenberg BM, Williams MA. Infectious complications of temporary spinal catheter insertion for diagnosis of adult hydrocephalus and idiopathic intracranial hypertension. Neurosurgery 2008;62(2):431–435; discussion 435–436. doi:10.1227/01.neu.0000316010.19012.35.

52 Braak H, Braak E. Frequency of stages of Alzheimer-related lesions in different age categories. Neurobiol Aging 1997;18(4):351–357.

53 Bech RA, Juhler M, Waldemar G, Klinken L, Gjerris F. Frontal brain and leptomeningeal biopsy specimens correlated with cerebrospinal fluid outflow resistance and B-wave activity in patients suspected of normal-pressure hydrocephalus. Neurosurgery 1997;40(3):497–502. doi:10.1097/0006123-199703000-00013.

54 Golomb J, Wisoff J, Miller DC, et al. Alzheimer's disease comorbidity in normal pressure hydrocephalus: prevalence and shunt response. J Neurol Neurosurg Psychiatry 2000;68(6): 778–781.

55 Holm A, Savolainen S, Alafuzoff I. Brain biopsy prior to treatment of Alzheimer's disease. Minim Invasive Neurosurg 2003;46(3):161–164. doi:10.1055/s-2003-40733.

56 Leinonen V, Koivisto AM, Savolainen S, et al. Amyloid and tau proteins in cortical brain biopsy and Alzheimer's disease. Ann Neurol 2010;68(4): 446–453. doi:10.1002/ana.22100.

57 Molde K, Söderström L, Laurell K. Parkinsonian symptoms in normal pressure hydrocephalus: a population-based study. J Neurol 2017;264(10): 2141–2148. doi:10.1007/s00415-017-8598-5.

58 Oravivattanakul S, Benchaya L, Wu GY, et al. Dopamine transporter (DaT) scan Utilization in a movement disorder center. Mov Disord Clin Prac 2016;3:31–35. doi:10.1002/mdc3.12261.

59 Odagiri H, Baba T, Nishio Y, et al. On the utility of MIBG SPECT/CT in evaluating cardiac sympathetic dysfunction in Lewy body diseases. PloS One 2016;11(4):e0152746. doi:10.1371/journal.pone.0152746.

60 Jagust WJ, Friedland RP, Budinger TF. Positron emission tomography with [18F] fluorodeoxyglucose differentiates normal pressure hydrocephalus from Alzheimer-type dementia. J Neurol Neurosurg Psychiatry 1985; 48(11):1091–1096. doi:10.1136/jnnp.48.11.1091.

61 Jeppsson A, Zetterberg H, Blennow K, Wikkelsø C. Idiopathic normal-pressure hydrocephalus: pathophysiology and diagnosis by CSF biomarkers. Neurology 2013;80(15):1385–1392. doi:10.1212/WNL.0b013e31828c2fda.

62 Agren-Wilsson A, Lekman A, Sjöberg W, et al. CSF biomarkers in the evaluation of idiopathic normal pressure hydrocephalus. Acta Neurol Scand 2007;116(5):333–339. doi:10.1111/j.1600-0404.2007.00890.x.

63 Kapaki EN, Paraskevas GP, Tzerakis NG, et al. Cerebrospinal fluid tau, phospho-tau181 and beta-amyloid1-42 in idiopathic normal pressure hydrocephalus: a discrimination from Alzheimer's disease. Eur J Neurol 2007;14(2): 168–173. doi:10.1111/j.1468-1331.2006.01593.x.

64 Xie L, Kang H, Xu Q, et al. Sleep drives metabolite clearance from the adult brain. Science 2013; 342(6156):373–377. doi:10.1126/science.1241224.

65 Graff-Radford NR. Alzheimer CSF biomarkers may be misleading in normal-pressure hydrocephalus. Neurology 2014;83(17):1573–1575. doi:10.1212/WNL.0000000000000916.

66 Sundström N, Lagebrant M, Eklund A, et al. Subdural hematomas in 1846 patients with shunted idiopathic normal pressure hydrocephalus: treatment and long-term survival. J Neurosurg 2017:1–8. doi:10.3171/2017.5.JNS17481.

67 Bruno A, Shah N, Lin C, et al. Improving modified Rankin Scale assessment with a simplified questionnaire. Stroke 2010;41(5):1048–1050. doi:10.1161/STROKEAHA.109.571562.

68 Hellström P, Klinge P, Tans J, Wikkelsø C. A new scale for assessment of severity and outcome in iNPH. Acta Neurol Scand 2012;126(4):229–237. doi:10.1111/j.1600-0404.2012.01677.x.

69 Kokmen E, Naessens JM, Offord KP. A short test of mental status: description and preliminary results. Mayo Clin Proc 1987;62(4):281–288. doi:10.1016/S0025-6196(12)61905-3.

70 Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975;12(3):189–198. doi:10.1016/0022-3956(75)90026-6.

71 Nasreddine ZS, Phillips NA, Bédirian V, et al. The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. J Am Geriatr Soc 2005;53(4):695–699. doi:10.1111/j.1532-5415.2005.53221.x.

72 Espay AJ, Da Prat GA, Dwivedi AK, et al. Deconstructing normal pressure hydrocephalus: ventriculomegaly as early sign of neurodegeneration. Ann Neurol 2017;82(2): 503–513. doi:10.1002/ana.25046.