DIAGNOSING IDIOPATHIC NORMAL-PRESSURE HYDROCEPHALUS

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OBJECTIVE: The precise incidence and prevalence of idiopathic normal-pressure hydrocephalus (INPH) is not known, and evidence-based clinical diagnostic criteria have not been developed previously. This report contains evidence-based guidelines for clinical diagnosis of INPH that are intended to facilitate future epidemiological studies of INPH, promote earlier and more accurate diagnosis, and ultimately improve treatment outcome.

METHODS: The criteria for the diagnosis of INPH are based on evidence from the medical literature, supplemented as necessary by expert opinion. From 1966 to 2003, 653 publications on "normal-pressure hydrocephalus" were cited in MEDLINE, including 29 articles that met the more stringent criteria of including "idiopathic normal-pressure hydrocephalus" in their title. Additional studies were considered that explicitly identified INPH cases and/or specified the criteria for a diagnosis of INPH. Studies were graded according to the class of evidence and results summarized in evidentiary tables. For issues of clinical relevance that lacked substantive evidence from the medical literature, the opinions of consulting experts were considered and contributed to "Options."

RESULTS: Evidence-based guidelines for the clinical diagnosis of INPH have been developed. A detailed understanding of the range of clinical manifestations of this disorder and adherence to practice guidelines should improve the timely and accurate recognition of this disorder.

CONCLUSION: It is recommended that INPH be classified into probable, possible, and unlikely categories. We hope that these criteria will be widely applied in clinical practice and will promote greater consistency in patient selection in future clinical investigations involving INPH.

KEY WORDS: Diagnosis, Idiopathic normal-pressure hydrocephalus, Normal-pressure hydrocephalus

RECOMMENDATIONS

Standards

There is no accepted standard for this topic.

Guidelines

The diagnosis of idiopathic normal-pressure hydrocephalus (INPH) requires convergent evidence from the clinical history, physical examination, and brain imaging. INPH typically manifests during adult life as an insidiously progressive, chronic disorder that lacks an identifiable antecedent cause. Gait and/or balance impairments are usual symptoms, and findings may also include disturbances in cognition and control of urination. Documentation of ventricular enlargement (e.g., Evan's index ≥0.3 or the equivalent) by brain imaging is necessary but not sufficient in itself to establish a diagnosis of INPH. The results of neuroimaging must be interpreted in conjunction with the clinical history and physical findings to accurately diagnose INPH and differentiate it from other disorders.

Options

When INPH is suspected but routine evaluations are inconclusive, certain supplemental tests may assist in the diagnostic process. These tests include neuropsychological testing, urodynamic studies, video- and computer-assisted

gait assessment, functional brain imaging, and other procedures. These test are not required routinely but may increase confidence in the diagnosis in selected cases.

A cerebrospinal fluid (CSF) opening pressure (CSF-OP) measured by lumbar puncture in the lateral recumbent position is useful in confirming that pressure is within the range expected for INPH (60–240 mm H_2O).

The diagnosis of INPH is complicated by the variability that exists in its clinical presentation and course. INPH can resemble, or occur in combination with, various disorders that are prevalent in the elderly, such as cerebrovascular disease, neurodegenerative disorders (e.g., Alzheimer's, Parkinson's, Lewy body disease), primary urological disorders, spinal stenosis, and other conditions. Accordingly, it may be useful to classify INPH into "probable," "possible," and "unlikely" categories, operationally defined by the extent to which the expected elements of INPH are present and diagnostic confounders can be excluded. "Shunt responsiveness" is considered separately as a measure of treatment outcome and does not enter into this diagnostic classification (see Part III).

OVERVIEW

Three and a half decades after Hakim and Adams (22) described the entity of "symptomatic occult hydrocephalus with 'normal' CSF pressure," the validity of the concept of INPH has been challenged (14, 18). The precise incidence and prevalence of INPH are not known, formal diagnostic criteria have not been developed, spinal fluid pressure is not truly normal, and the natural history of untreated INPH has not been studied systematically. Nevertheless, it would do a great disservice to many patients not to acknowledge the existence of the INPH syndrome when its potentially incapacitating symptoms can be improved or even cured by shunt placement. The ataxia, dementia, and incontinence associated with more advance stages of INPH tend to be less responsive to treatment than milder symptoms of less than 2 years' duration (36). Thus, early and accurate diagnosis of INPH can be instrumental in achieving an optimal treatment outcome and avoiding potentially severe and irreversible impairments.

Advances in INPH research and clinical practice have been hampered by the lack of widely accepted, standardized criteria for its diagnosis. Various authors have described systematic means of selecting INPH cases for inclusion in studies (3, 9, 45, 46). Although these criteria have merit, they are neither evidence-based nor supported by a broad consensus. As a consequence, they have not been widely adopted in practice by clinicians or investigators. Compounding this problem, there are no generally accepted neuropathological criteria for postmortem confirmation of a diagnosis of INPH. Discrete abnormalities, such as arachnoid fibrosis, have been reported on brain autopsies of selected patients with INPH but occur too infrequently to be useful in validating clinical diagnosis (2).

Diagnostic sensitivity for INPH is reduced by the variability that exists in its clinical presentation and course. Diagnostic specificity is reduced owing to the common occurrence of other conditions in the elderly, such as cerebrovascular disease and certain neurodegenerative disorders, with symptoms closely resembling those of INPH. In addition, although INPH can readily be distinguished from several other conditions that involve ventricular enlargement, these distinctions are not made consistently in actual practice. For example, adult age of onset can be used to distinguish INPH from childhood-onset forms of hydrocephalus. Secondary hydrocephalus can be differentiated from INPH by virtue of its identifiable precipitants. Cerebral atrophy cannot predominate in INPH as it does in so-called "hydrocephalus ex vacuo." Reduced flow through the aqueduct of Sylvius is a distinguishing feature of aqueductal stenosis, whereas macroscopic blockage of the ventricular system is characteristic of noncommunicating hydrocephalus. In the recently described syndrome of long-standing overt ventriculomegaly in adults, enlargement of head circumference and/or destruction of the sella turcica are obligate features required for diagnosis (34). Although all of these disorders have some features in common with INPH, they can follow a very different course or require different management strategies. The clinical features and prognosis in INPH are sufficiently unique for it to be considered a discrete clinical syndrome warranting its own diagnostic and management guidelines.

Certain authors (35) have suggested that the only reliable means of validating a diagnosis of INPH is to document a positive response to shunt placement. However, this approach would yield an unacceptable rate of incorrect diagnostic classifications. False-negatives would occur when patients with true INPH have an absent or diminished response to shunt placement owing to coexisting conditions (e.g., Alzheimer's, Parkinson's, cerebrovascular disease, etc.), postoperative complications (e.g., subdural hematomas, infections), inadequate treatment (e.g., overdrainage or underdrainage), or mechanical failures (e.g., shunt malfunction). False-positive diagnoses result because patients with similar conditions, such as aqueductal stenosis, secondary NPH, and noncommunicating hydrocephalus, often respond favorably to shunt placement and because placebo responses sometimes occur (23). Studies have reported that prolonged positive response occurred in as few as 29% of INPH cases, suggesting that there may be a poor correlation between shunt responsiveness and the selection criteria now used in INPH studies. For these and other reasons, shunt responsiveness should not be used as the basis for diagnosis of INPH.

A large number of test procedures, invasive and noninvasive, have been developed to assist in the diagnosis of and prognostication about INPH. Nevertheless, INPH is routinely diagnosed on the basis of convergent evidence from clinical history, examination, and brain imaging. Additional tests may improve diagnostic confidence, promote differential diagnosis, or assist in prognosticating about response to shunt placement. However, no single test in isolation has been found to supplant the combination of clinical assessment and neuroimaging as the basis for diagnosis of INPH. The association

TABLE 2.1. Description of idiopathic normal-pressure hydrocephalus classification: Probable, possible, and unlikely categories[a]

Probable INPH

The diagnosis of Probable INPH is based on clinical history, brain imaging, physical findings, and physiological criteria.

I. History

Reported symptoms should be corroborated by an informant familiar with the patient's premorbid and current condition, and must include
  a. Insidious onset (versus acute)
  b. Origin after age 40 yr
  c. A minimum duration of at least 3 to 6 mo
  d. No evidence of an antecedent event such as head trauma, intracerebral hemorrhage, meningitis, or other known causes of secondary hydrocephalus
  e. Progression over time
  f. No other neurological, psychiatric, or general medical conditions that are sufficient to explain the presenting symptoms

II. Brain imaging

A brain imaging study (CT or MRI) performed after onset of symptoms must show evidence of
  a. Ventricular enlargement not entirely attributable to cerebral atrophy or congenital enlargement (Evan's index >0.3 or comparable measure)
  b. No macroscopic obstruction to CSF flow
  c. At least one of the following supportive features
    1. Enlargement of the temporal horns of the lateral ventricles not entirely attributable to hippocampus atrophy
    2. Callosal angle of 40 degrees or more
    3. Evidence of altered brain water content, including periventricular signal changes on CT and MRI not attributable to microvascular ischemic changes or demyelination
    4. An aqueductal or fourth ventricular flow void on MRI

Other brain imaging findings may be supportive of an INPH diagnosis but are not required for a Probable designation
  1. A brain imaging study performed before onset of symptoms showing smaller ventricular size or without evidence of hydrocephalus
  2. Radionuclide cisternogram showing delayed clearance of radiotracer over the cerebral convexities after 48–72 h
  3. Cine MRI study or other technique showing increased ventricular flow rate
  4. A SPECT-acetazolamide challenge showing decreased periventricular perfusion that is not altered by acetazolamide

III. Clinical

By classic definitions (Fisher [17], Hakim [22], etc.), findings of gait/balance disturbance must be present, plus at least one other area of impairment in cognition, urinary symptoms, or both.

With respect to gait/balance, at least two of the following should be present and not be entirely attributable to other conditions
  a. Decreased step height
  b. Decreased step length
  c. Decreased cadence (speed of walking)
  d. Increased trunk sway during walking
  e. Widened standing base
  f. Toes turned outward on walking
  f. Retropulsion (spontaneous or provoked)
  g. *En bloc* turning (turning requiring three or more steps for 180 degrees)
  h. Impaired walking balance, as evidenced by two or more corrections out of eight steps on tandem gait testing

With respect to cognition, there must be documented impairment (adjusted for age and educational attainment) and/or decrease in performance on a cognitive screening instrument (such as the Monumental State examination), or evidence of at least two of the following on examination that is not fully attributable to other conditions
  a. Psychomotor slowing (increased response latency)
  b. Decreased fine motor speed
  c. Decreased fine motor accuracy
  d. Difficulty dividing or maintaining attention
  e. Impaired recall, especially for recent events
  f. Executive dysfunction, such as impairment in multistep procedures, working memory, formulation of abstractions/similarities, insight
  g. Behavioral or personality changes

To document symptoms in the domain of urinary continence, either one of the following should be present
  a. Episodic or persistent urinary incontinence not attributable to primary urological disorders
  b. Persistent urinary incontinence
  c. Urinary and fecal incontinence

TABLE 2.1. Continued

Or any two of the following should be present
    a. Urinary urgency as defined by frequent perception of a pressing need to void
    b. Urinary frequency as defined by more than six voiding episodes in an average 12-hour period despite normal fluid intake
    c. Nocturia as defined by the need to urinate more than two times in an average night

IV. Physiological

CSF opening pressure in the range of 5–18 mm Hg (or 70–245 mm H_2O) as determined by a lumbar puncture or a comparable procedure. Appropriately measured pressures that are significantly higher or lower than this range are not consistent with a probable NPH diagnosis.

Possible INPH

A diagnosis of Possible INPH is based on historical, brain imaging, and clinical and physiological criteria

I. History

Reported symptoms may
    a. Have a subacute or indeterminate mode of onset
    b. Begin at any age after childhood
    c. May have less than 3 mo or indeterminate duration
    d. May follow events such as mild head trauma, remote history of intracerebral hemorrhage, or childhood and adolescent meningitis or other conditions that in the judgment of the clinician are not likely to be causally related
    e. Coexist with other neurological, psychiatric, or general medical disorders but in the judgment of the clinician not be entirely attributable to these conditions
    f. Be nonprogressive or not clearly progressive

II. Brain imaging

Ventricular enlargement consistent with hydrocephalus but associated with any of the following
    a. Evidence of cerebral atrophy of sufficient severity to potentially explain ventricular size
    b. Structural lesions that may influence ventricular size

III. Clinical

Symptoms of either
    a. Incontinence and/or cognitive impairment in the absence of an observable gait or balance disturbance
    b. Gait disturbance or dementia alone

IV. Physiological

Opening pressure measurement not available or pressure outside the range required for probable INPH

Unlikely INPH
    1. No evidence of ventriculomegaly
    2. Signs of increased intracranial pressure such as papilledema
    3. No component of the clinical triad of INPH is present
    4. Symptoms explained by other causes (e.g., spinal stenosis)

[a] INPH, idiopathic normal-pressure hydrocephalus; CT, computed tomography; MRI, magnetic resonance imaging; CSF, cerebrospinal fluid; SPECT, single-photon emission computed tomography.

between noncommunicating, nonatrophic ventricular enlargement and the triad of gait, cognitive, and sphincteric disturbances has been observed in many clinical studies over the past 3 decades. Patients with ventriculomegaly in the absence of any of the symptoms are generally not considered to have INPH (31). Previously proposed diagnostic guidelines for INPH have placed a primacy on identifying the subset of patients most likely to respond to shunt treatment. In contrast, shunt responsiveness does not enter into this diagnostic formulation and is considered separately (see Part III). Likewise, patients without evidence of ventricular enlargement are gen-

erally not treated for INPH, even if they manifest some or all of the other signs and symptoms typically associated with this disorder. The diagnosis of INPH therefore requires the convergence of a particular set of clinical and brain imaging findings.

To acknowledge that different degrees of diagnostic certainty follow routine assessments in different cases, a classification system of "probable," "possible," and "improbable" INPH has been proposed (45). The present consensus criteria distinguish between basic findings required for the diagnosis of INPH and adjunctive measures that may support a diag-

TABLE 2.2. Evidentiary data: Diagnosing idiopathic normal-pressure hydrocephalus[a]

Series (ref. no.)	INPH	Description	Class	Conclusion
Hakim and Adams, 1965 (22)	1	This article is included for historical purposes because it introduced the concept of INPH. Three cases were presented, two secondary and one INPH. In each case, impaired consciousness and reduced responsiveness of various degree was observed, with alteration of gait. Incontinence and dementia and ventriculomegaly with lumbar pressure ranging from 130 to 180 mm H_2O were observed. Lowering of the pressure by serial lumbar punctures or performing a V-A shunt surgery resulted in clinical improvement.	N/A	It was concluded that the effective expansile force within the ventricles is not equal to the intraventricular pressure but is a product of ventricular pressure and area. This expansile force played a role in compression and stretching of the major long tracts in the cerebral white matter and corpus callosum, resulting in a physiological block of function, which, to some extent, was reversible by reducing the pressure.
Black, 1980 (5)	62	Criteria for shunt surgery of 62 INPH patients included clinical triad of gait disturbance, memory difficulty, and urinary incontinence. Enlarged ventricles on CT scan and lumbar puncture pressure less than 180 mm H_2O were also required.	III	Having the classic triad of INPH appears to increase the chance of improvement after shunt surgery. Ventriculomegaly and mild atrophy on CT scan predicted improvement in 11 of 13 patients (84.6%). Complication rate was 35.4%.
Boon et al., 1997 (9)	95	A multicenter study of NPH in which patients were followed up for 1 year. Scales were developed for scoring gait disturbance and dementia. CT scan with an Evans' index >0.3 and a ventricular index >0.8 coupled with the sum of the four largest sulci at the convexity, measured at the two upper CT slices, being <25 millimeter was classified typical of NPH. The resistance to outflow of CSF >18 mm Hg/ml/min was designated as a positive test outcome.	II	The accurate predictive value of the combination of the clinical and CT findings was 0.65. The positive results of outflow resistance, clinical, and CT findings was 0.74. Typical clinical symptoms and CT evidence of NPH is important in predicting shunt outcome. The measurement of CSF outflow resistance increases the number of shunt responders.
Jonas and Brown, 1975 (24)	4	Five patients of whom four had INPH were evaluated by urological procedures. The bladder difficulties observed were urinary frequency and urgency incontinence. Cystometry was believed to be the key study. Findings were those of the so-called "uninhibited neurogenic bladder," in which there is loss of inhibitory impulses from descending tracts. With loss of inhibitory impulses, the bladder contracts, resulting in frequent voidings.	III	Bladder dysfunction related to dementia or gait difficulty was eliminated in this study. The study supported the possibility that bladder dysfunction in INPH is neurogenic. Identification of the sites within the nervous system where the dysfunction arose could not be made.
Petersen et al., 1985 (36)	45	Retrospective study of 45 patients with INPH who had undergone a shunting procedure during a 16-yr period. Patients were evaluated on initial symptoms, duration of symptoms, ADL status, CT scans, CSF cisternograms, and EEGs. Of the 45 patients, 25 had the triad of INPH symptoms. All other patients had at least gait disorder; 30 patients had CT scans that showed large ventricles and minimal cortical atrophy without evidence of obstruction to CSF flow. There were no other pathological changes. Fifteen patients did not have CT scans before surgery because they were shunted before the introduction of CT scans. Instead, they underwent radioisotope CSF cisternography. Follow-up period after the surgery ranged from 10 to 157 mo.	III	Patients who had initial gait disturbance of <2 yr were most likely to improve (74%). This is followed by improvement in incontinence (65%) and dementia (57%). CT scan played an important role in the diagnosis and follow-up. Twenty five of the 30 patients (83%) who had preoperative CT scans improved after the surgery. Conversely, 9 of the 15 patients (60%) who did not have preoperative CT scans improved. The improvement (83 versus 60%) was achieved with the help of CT scans, the experience of the clinician, and the positive ancillary tests. Complication rate was 30%.
Vanneste et al., 1993 (45)	89	A retrospective study of combined clinical and CT data was used to create an ordinal global scale to predict the clinical outcome of 112 shunted patients for presumed NPH, of which 89 were INPH. The clinical and CT findings were used to define the categories of probable, possible, and improbable SR-NPH patients.	III	Probable SR-NPH group had an overall improvement of 58% (95% CI, 37–77%). Shunting patients of improbable SR-NPH would have led to improvement in 13% (95% CI, 4–27%). The best strategy was to shunt probable SR-NPH, which would have led to predictive accuracy of 75% (95% CI, 66–84%). The study illustrated the need to assess the pretest probability of NPH based on clinical and CT findings before establishing the clinical usefulness of ancillary tests.

TABLE 2.2. Continued

Series (ref. no.)	INPH	Description	Class	Conclusion
Stolze et al., 2000 (41)	10	Precise gait analysis was performed in 10 patients and 12 age-matched healthy controls during over-ground and treadmill locomotion. All patients had a moderate to severe gait impairment. Memory problems and urinary incontinence were also present with accompanying ventriculomegaly in the presence of moderate or severe cortical atrophy. Compared with healthy individuals, NPH patients walked more slowly, with shorter steps and with a lower cadence. Step width and foot rotation angles were significantly increased in NPH. Patients were tapped 30 ml CSF, and gait was evaluated before CSF tapping and 24 h after tapping.	II	Typical features of NPH gait were reported as decreased stride length, decreased foot to floor clearance, and a broad-based gait. Only the stride length improved after a diagnostic CSF tap.
Krauss et al., 1997 (26)	65	One hundred eighteen patients with symptomatic adult hydrocephalus were studied. Hydrocephalus was categorized as INPH in 65 patients (55%), secondary NPH in 15 (13%), noncommunicating/aqueductal stenosis in 5 (4%), and atrophic/other in 33 (28%). Of 118 patients, 88 (75%) had additional akinetic, tremulous, hypertonic or hyperkinetic movement disorders. Most frequent movement disorder was bradykinesia. The prevalence was highest in INPH patients (86%) compared with secondary NPH (66%) and with noncommunicating hydrocephalus (40%). Movement disorders that were not attributable to any other cause were also highest in INPH (68%). Prevalence of parkinsonism was 14% in INPH. In 55% of these patients, parkinsonism was caused by their active hydrocephalus.	II	Akinetic symptoms and parkinsonian features of NPH were found to be improved after shunting.

[a] INPH, idiopathic normal-pressure hydrocephalus; N/A, not applicable; V-A, ventriculoatrial; CT, computed tomographic; CSF, cerebrospinal fluid; ADL, activities of daily living; EEG, electroencephalogram; SR, shunt-responsive; V-P, ventriculoperitoneal; CI, confidence interval; CBF, cerebral blood flow; Ro, CSF resistance.

nosis of INPH. A description of the probable, possible, and unlikely INPH entities is presented in *Table 2.1*, and these categories have been modified on the basis of contributions from the work of other investigators. Prospective validation of these criteria will require studies of interrater reliability, construct validity, sensitivity, and specificity, as well as correlation with shunt responsiveness. It is our hope that the formulation of consensus criteria will promote improved clinical recognition of INPH and stimulate additional research about this syndrome.

PROCESS

The criteria for the diagnosis of INPH described here are based on evidence from the medical literature, supplemented as necessary by expert opinion. From 1966 to 2003, 653 publications on "normal-pressure hydrocephalus" were cited in MEDLINE, including 29 articles that met the more stringent criteria of including "idiopathic normal-pressure hydrocephalus" in their title (see Evidentiary Data, *Table 2.2*). Additional studies were considered that explicitly identified cases of INPH and/or specified the criteria for a diagnosis of INPH. Studies were graded according to the class of evidence and results summarized in evidentiary tables. For issues of clinical relevance that lacked substantive evidence from the medical literature, the opinions of consulting experts (see Part I) were considered and contributed to "options."

SCIENTIFIC FOUNDATION

Features of INPH Derived from Clinical History

Evaluations of suspected INPH are typically performed by neurosurgeons, neurologists, psychiatrists, geriatricians, and/or internists (3). INPH may be suspected as a result of incidental findings of ventriculomegaly on a brain imaging study performed for other purposes. In other cases, clinical complaints trigger suspicion of INPH. INPH should be considered in the differential diagnosis of any unexplained disturbance of gait, continence, and cognition that begins insidiously in an adult. This is most commonly a gait disturbance, followed in frequency by cognitive impairments and least often, urinary incontinence (9, 10).

Patients with INPH may have impairments of insight and/or memory that impede their ability to provide an accurate personal history. In cases of suspected INPH involving cognitive impairment, it is therefore important to obtain the clinical history from both the patient and a knowledgeable informant who is familiar with the patient's premorbid and current levels of function. When eliciting the history, particular attention should be paid to the mode of onset of symptoms

(acute, subacute), their temporal course (static, progressive), and their severity (mild, moderate, severe). Special emphasis should be placed on symptoms involving gait, balance, cognition, and urinary continence.

By definition, INPH (in contrast to secondary NPH) is not the product of a discrete brain injury. As part of the clinical interview, inquiries should be made about possible precipitating factors, such as head trauma, meningitis/encephalitis, and intracerebral hemorrhage. In a patient with communicating hydrocephalus, documentation of these events makes a diagnosis of secondary NPH more likely, particularly if the onset temporally preceded or correlated with the development of symptoms. Familial occurrence of INPH is rarely observed (in contrast to congenital hydrocephalus). Nevertheless, it is recommended that elements of the family history be assessed, with emphasis on neurodegenerative disorders such as Parkinson's disease, Alzheimer's disease, and Huntington's disease, as well as other neurological/psychiatric conditions that have heritable components and could resemble or coexist with INPH. Psychiatric symptoms have been attributed to INPH, and preexisting psychiatric disturbances may be exacerbated in its course. Family and personal histories of psychiatric disturbances should therefore be reviewed, and inquiries should also be made about neurovegetative signs (disturbances of sleep, appetite, libido, motivation).

Documentation of symptoms involving control of urination is important, because in-office assessment of urinary function is usually limited unless a urological referral is made. Patients should be encouraged to document their urinary symptoms for a period of at least 1 week, noting frequency of urination, episodes of urinary urgency, nocturia, and frank incontinence (24).

The differential diagnosis of INPH (*Table 2.3*) includes a large number of conditions that are relatively commonplace in the elderly. A review of past medical and surgical history is therefore an important part of the evaluation. Cerebrovascular disease and its risk factors are among the most important of these conditions (10). Hypertension has been reported, in some cases, to develop in parallel with symptomatic INPH. Common disorders that affect gait in the elderly and may complicate the diagnosis of INPH include spinal stenosis, peripheral neuropathy, and vestibular problems. Prostatism in men and chronic urinary tract infections in women can cause symptoms similar to those of INPH and should be excluded as the cause of urinary symptoms.

Features of INPH Derived from Brain Imaging

As part of the routine evaluation of suspected INPH, a brain imaging study (typically magnetic resonance imaging [MRI] or computed tomography [CT]) must be performed to assess ventricular size and to rule out ventricular obstruction. Ventricular enlargement is documented by an Evan's index of 0.3 or greater or an equivalent measure reflecting an increased ratio of ventricular size to cranial diameter (16).

TABLE 2.3. Conditions that may present similarly to idiopathic normal-pressure hydrocephalus or present comorbidly (based on Bech-Azeddine et al., 2001 [3] and expert opinion)

Neurodegenerative disorders
Alzheimer's disease
Parkinson's disease

Vascular dementia
Cerebrovascular disease
Stroke
Multi-infarct state
Binswanger's disease
Cerebral autosomal dominant arteriopathy, subcortical infarcts, and leukoencephalopathy
Vertebrobasilar insufficiency

Other hydrocephalus disorders
Aqueductal stenosis
Arrested hydrocephalus
Long-standing overt ventriculomegaly syndrome
Noncommunicating hydrocephalus

Neurodegenerative disorders
Alzheimer's disease
Parkinson's disease
Lewy body disease
Huntington's disease
Frontotemporal dementia
Corticobasal degeneration
Progressive supranuclear palsy
Amyotrophic lateral sclerosis
Multisystem atrophy
Spongiform encephalopathy

Infectious diseases
Lyme
Human immunodeficiency virus
Syphilis

Urological disorders
Urinary tract infection
Bladder or prostate cancer
Benign prostatic enlargement

Miscellaneous
B_{12} deficiency
Collagen vascular disorders
Epilepsy
Depression
Traumatic brain injury
Spinal stenosis
Chiari malformation
arrested hydrocephalus
Wernicke's encephalopathy
Carcinomatous meningitis
Spinal cord tumor

MRI is more expensive than CT and cannot be administered to patients with certain pacemakers, ferromagnetic metallic implants, or severe claustrophobia. Yet, MRI offers several advan-

tages over CT, including more ready evaluation of such coexisting conditions as cerebrovascular disease and the opportunity to detect findings that correlate positively with the presence of INPH. For example, MRI permits detection of a smooth periventricular halo that can be indicative of altered brain water content, as has been documented to occur in both noncommunicating and communicating hydrocephalus. Fluid-attenuated inversion recovery sequences accentuate leukoareosis and can be useful in assessing the burden of white matter disease associated with INPH. Aqueductal flow voids can also be observed, arising from a signal artifact created by hyperdynamic CSF flow through the cerebral aqueduct. Sagittal MRI permits measurement of the diameter of the corpus callosum, which decreases in many cases of INPH as the dorsal surface of the ventricle domes upward (13). Coronal MRI permits calculation of the callosal angle, which may be increased in INPH, and permits assessment of the perihippocampal morphology, which may be useful in distinguishing ventriculomegaly secondary to cerebral atrophy (which may expose sulcal markings in this area) from hydrocephalic enlargement of the ventricle, as occurs in INPH (which obliterates perihippocampal sulcal markings). Although MRI is useful for revealing these supportive findings, these are not diagnostic of INPH in their own right. Either CT or MRI can document noncommunicating ventriculomegaly sufficient to satisfy the brain imaging requirements for routine diagnosis of INPH. Diagnosis can be made on the basis of CT findings alone.

Several other brain imaging techniques have been studied as potential adjuncts to the diagnosis of INPH, but at present, none have been proven to increase diagnostic accuracy beyond routine structural brain imaging. Functional imaging techniques, including perfusion imaging with single-photon emission computed tomography (SPECT) and SPECT/acetazolamide challenge, resting metabolic imaging with positron emission tomography, and nuclear cisternography are not recommended as part of the routine evaluation of suspected INPH. Positron emission tomography and SPECT may be abnormal in INPH, but the diagnostic value of these techniques has not been established.

Clinical Symptoms of INPH

There is considerable variation in the nature, severity, and course of progression of the symptoms of INPH. The natural history of untreated INPH has not been well characterized, and it is not clear whether all cases ultimately progress, nor is the tempo of progression established for the majority of cases. Progression of symptoms is generally expected but may not be uniform over the course of the disease. Symptoms of INPH in the early stage and late stages of the disease may differ dramatically, as may symptoms in previously treated versus untreated patients.

All three components of the so-called classic triad of INPH need not be present for the diagnosis of INPH to be made. Gait disturbance tends to be the most readily recognized feature of INPH. Cognitive disturbances do not occur in all patients, and the severity of cognitive and motor symptoms does not necessarily correlate at baseline or progress in parallel. Incontinence in INPH is difficult to distinguish from urinary symptoms associated with other common disorders. The signs and symptoms of INPH are typically bilateral but may appear lateralized when superimposed on coexisting conditions, such as stroke, radiculopathy, and peripheral neuropathy.

Movement Disorders

Gait

Early descriptions emphasized cognitive symptoms as the primary clinical manifestation of NPH. Ojemann et al. (35) were among the first to report that gait disturbance could be an initial manifestation of NPH. Fisher (17) later documented that among 16 patients with successfully shunted NPH, gait disturbance preceded dementia in 12 and was affected concomitantly in 3. Only 1 patient in that series had dementia as the initial manifestation. However, because cognitive symptoms of INPH can be subtle and may go undetected unless tested formally, it remains to be seen whether gait disturbance is an earlier symptom or more prevalent than dementia in a majority of cases.

The origin of the gait disturbance in INPH is not entirely understood. An early hypothesis suggested that enlargement of the ventricles in INPH led to compression and/or deformation of the upper motor neuron fibers passing through the medial portion of the corona radiata. Although pyramidal tract involvement is not supported by a recent study using motor evoked responses (3), involvement of premotor pathways has not been ruled out. Electromyographic evidence reveals contraction of antagonistic muscle groups and abnormally increased activity in the antigravity muscles acting on hip and knee joints (2, 9). This suggests that the gait disorder of INPH is a disturbance in the phased activation of muscle groups, as would be seen in a disorder of subcortical motor control rather than a primary pyramidal tract disturbance. With progression of INPH and/or the evolution of extensive subcortical white matter changes, pyramidal tract involvement may become more likely. Although flexor plantars are typically observed early in the course of INPH, reflex changes, including extensor plantar responses, may be expected at later stages. A possible contribution of subcortical dopaminergic pathways to the gait and movement disturbances is discussed below in the section on other movement disorders associated with INPH.

Detailed studies of the gait of patients with clinically diagnosed and radiologically confirmed INPH reveal several characteristics that may be useful in the clinical differential diagnosis of INPH. The pattern of gait seen in INPH patients has been variably described as "apractic," "bradykinetic," "glue-footed," "magnetic," "parkinsonian," "short-stepped," and "shuffling." Gait problems may emerge as difficulty in ascending or descending stairs and curbs and in walking at the expected pace. Patients may complain of difficulty rising from a chair, "give-way" weakness of the lower extremities, and fatigue brought on by walking. As the disease progresses, turning in place becomes tenuous and typically requires multiple steps (*en bloc*). Weakness of the legs is not usually evident on neurological examination in such patients, and pyramidal dysfunction is therefore not considered a common symptom of INPH.

Computerized analysis of the gait of INPH patients has shown 1) reduced cadence, 2) decreased step height, and 3)

reduced counterrotation of the shoulders relative to the pelvis during walking. The upward angular movement of the foot during stepping is inadequate in INPH, and stride length is diminished. The step width and foot rotation angles are reportedly increased, and there is less step-to-step variability in these parameters than in normal controls (35).

The gait findings in INPH may coexist with other conditions but should not be entirely attributable to structural lesions of the brain or spine (such as tumors, strokes, vascular malformation, stenosis, etc.), systemic medical conditions (such as infections, metabolic abnormalities, inflammatory disorders, cancer), or neurodegenerative conditions (idiopathic Parkinson's disease, amyotrophic lateral sclerosis, etc.) (*Table 2.3*).

Posture

Disturbance of both gait and stance were recognized early in the history of NPH research, giving rise to the term "hydrocephalic astasia-abasia" (17). The stance in INPH may be more forward leaning than in healthy normal individuals, and INPH patients tend to show a wider sway and imbalance that may be accentuated by eye closure (6, 48).

Other Movement Disorders, Including Parkinsonism

Other movement disorders may be as common as the widely recognized gait disturbance of INPH. Apraxias of limb and trunk movements, particularly in the vertical direction, are commonly observed. INPH patients sometimes show a dramatic inability to ascend onto the examining table or climb into their own bed at home. Once recumbent, they may have great difficulty turning or shifting their position without assistance or simulating walking movements while recumbent.

Akinetic, tremulous, hypertonic, or hyperkinetic movement disorders have been described in NPH patients and may be seen more frequently in patients with idiopathic forms of the disorder (26). Bradykinesia affects the upper extremities in the form of slow movement in as many as half of NPH patients, whereas frank parkinsonism has been reported as a symptom of NPH in as many as 11% of patients (25).

The plausibility of an association between NPH and Parkinson's disease in humans is supported by the creation of reversible parkinsonian symptoms in animal models of hydrocephalus (43). Symptoms consistent with parkinsonism that have been reported to occur in NPH include bradykinesia, tremor, rigidity with or without cogwheeling, decreased arm swing, shuffling gait, festination, retropulsion, masked facies, hypophonia, decreased eye blink rate, difficulty initiating movements, postural instability, dyssynergia, and drooling. Cognitive symptoms resembling the dementia seen in some patients with idiopathic Parkinson's disease have also been described in association with INPH, as have frontal release signs such as snout and grasp responses. Parkinson's disease-like symptoms in INPH patients may be L-dopa-responsive or -unresponsive and may or may not respond dramatically to shunt placement. One mechanism that has been postulated for parkinsonian symptoms in INPH is compromise of nigrostriatal dopaminergic pathways brought about by abnormal pulsatile CSF flow affecting the sub-

stantia nigra and/or striatum, causing a disturbance in motor planning (42).

Although incontinence is one of the originally described features of INPH, it is the least well characterized. Increased frequency and urgency without actual urinary incontinence may be seen in early stages of the disorder, with progression to frank urinary incontinence with disease progression. Incontinence is not an invariable component of the disorder and may occur rarely or just intermittently in some cases. Fecal incontinence is not a usual presenting symptom of INPH, although it may well develop later in the course of the disorder, particularly if it is left untreated.

Patients in more advanced stages of INPH may show indifference to the episodes of incontinence, suggesting that the incontinence is associated with frontal executive dysfunction. In other patients, gait disturbance, apraxia, and bradykinesia may act to physically restrain the individual from performing successful toileting. This results in functional incontinence despite retained insight, normal sensation of bladder fullness, or otherwise normal bladder function.

The term "neurogenic bladder syndrome" has been used in association with NPH (43). Hyperactivity of the urinary bladder can be detected by urodynamic studies in some cases (19, 41), with strong contractions elicited by infusions of small volumes of fluid into the bladder. Urodynamic studies may be helpful in distinguishing INPH-related frequency, urgency, and incontinence from common comorbid conditions in the age groups most prone to develop INPH, such as prostatism in men, recurrent urinary tract infections in women, and bladder dystonia/dysautonomia in either sex.

Cognitive and Behavioral Manifestations

Dementia

The principal cognitive symptoms seen in INPH are suggestive of a subcortical dementing process, including slowing of thought, inattentiveness, and apathy, as well as encoding and recall problems (30). True aphasia is unusual in INPH, although speech output may be disturbed secondary to dysexecutive or motivational problems. The locus of dysfunction responsible for dementia in INPH remains unclear, although the frontostriatal system has been implicated by some investigators. Others emphasize the importance of other subcortical structures, including projection fibers passing in proximity to the lateral ventricles. The severity of cognitive impairments seen in INPH encompasses a full spectrum from minimally detectable to profoundly severe. In mild stages, differential diagnosis may be particularly difficult owing to overlap of INPH-related cognitive impairment with that seen in more prevalent disorders, such as Alzheimer's disease. This overlap occurs because patients with Alzheimer's disease have presenting problems in multiple cognitive domains. The essential criteria for clinical diagnosis of Alzheimer's disease is included in *Table 2.4*, and a comparison of cognitive deficits with Alzheimer's disease and INPH is presented in *Table 2.5*. As INPH progresses, cognitive impairments may become more generalized and more refractory to treatment. Nevertheless, even

TABLE 2.4. Essentials of National Institute of Neurological Diseases and Blindness-Alzheimer's Disease and Related Disorders Association criteria for clinical diagnosis of Alzheimer's disease (29)

Criteria for clinical diagnosis of probable Alzheimer's disease
Dementia established by clinical examination and documented (by mental status tests) and confirmed by neuropsychological tests
Deficits in two or more areas of cognition
Progressive worsening of memory and other cognitive functions
No disturbances in consciousness
Onset between ages 40 and 90 yr
Absence of systemic disorders or other brain diseases that in and of themselves could account for progressive deficits in memory and cognition

Features that make Alzheimer's disease uncertain or unlikely
Sudden, apoplectic onset
Focal neurological findings such as hemiparesis, sensory loss, visual field deficits, and in coordination early in the course of the illness
Seizures or gait disturbances at the onset or very early in the course of the illness

Criteria for clinical diagnosis of possible Alzheimer's disease
May be made on the basis of the dementia syndrome, in the absence of other neurological, psychiatric, or systemic disorders sufficient to cause dementia, and in the presence of variations in the onset, presentation, or clinical course
May be made in the presence of a second systemic or brain disorder sufficient to produce dementia, which is not considered to be the cause of the dementia
When a single, gradually progressive severe cognitive deficit is identified in the absence of other identifiable causes

TABLE 2.5. Comparison of cognitive deficits in Alzheimer's disease and idiopathic normal-pressure hydrocephalus

Cognitive skills	Alzheimer's disease	Idiopathic normal-pressure hydrocephalus
Impaired	Memory	Psychomotor slowing
	Learning	Fine motor speed
	Orientation	Fine motor accuracy
	Attention concentration	
	Executive functions	
	Writing	
Borderline impairment	Motor and psychomotor skills	Auditory memory (immediate and delayed)
	Visuospatial skills	Attention concentration
	Language	Executive function
	Reading	Behavioral or personality changes

patients with fairly advanced dementia may still respond positively to shunt placement (4).

When possible, quantifiable measures of cognitive performance (neuropsychological tests) should be used. The impairments detected should not be attributable to other conditions such as neurodegenerative disorders, stroke, head trauma, psychoactive medications, or other identifiable factors.

Psychiatric Manifestations

Although cognitive changes such as memory impairment, attentional disturbances, and bradyphrenia are usually cited as the main features of the dementia associated with INPH, behavioral disturbances have also been reported. Case reports of a variety of psychiatric disorders in association with INPH have appeared, including depression (38, 39), mania (bipolar disorder) (4, 40), aggressivity (15, 28), obsessive compulsive disorder (1), psychosis including paranoia and hallucinations (7, 27, 37), and disturbance of impulse control (21).

The appearance of symptoms of depression in patients with INPH could be a neurochemical consequence of the underlying brain disorder. However, it could also arise in response to the physical and mental disabilities associated with INPH. An additional possibility is that what seems to be depression is actually a look-alike syndrome brought about by the psychomotor retardation and cognitive changes commonly seen in INPH. Whatever the pathogenesis, psychiatric presentations in INPH are important to recognize, both because they may complicate clinical diagnosis and because they may be refractory to conventional pharmacological interventions and respond more favorably to shunt treatment in some cases.

Other Symptoms of NPH and Symptoms Not Expected

Case reports and case series have reported a variety of symptoms that represent infrequently seen but reproducibly

observed correlates of INPH. Examples include syncopal episodes (32), restructuring of the sleep architecture (33), a possible association with systemic hypertension (44), oculomotor abnormalities (47), and endocrine disturbances (30). Sensory changes have been reported in INPH patients and may be described as stiffness and/or aching numbness that affects the lower extremities predominantly, occasionally involving the hands (17). These and other isolated signs and symptoms occur infrequently in patients with INPH; their reported resolution with shunt placement in some patients provides circumstantial evidence for a causal relationship between their occurrence and INPH.

Although a broad spectrum of signs and symptoms has been reported in association with INPH, certain symptoms would not be expected. For example, papilledema would not be expected in INPH, because elevations in intracranial pressure sufficient to cause papilledema would be inconsistent with the normal range of intracranial pressures expected in this disorder. Seizures occur with some frequency after shunting but do not seem to be a common presenting symptom of INPH. Likewise, headaches are unusual as a manifestation of INPH, although they may occur for other reasons in persons in the age group at risk for INPH.

Measurement of CSF-OP

The concept that a "normal" CSF pressure is a defining feature of INPH has been criticized (12, 14). In normal volunteers, the CSF-OP averages 122 ± 34 mm H_2O (8.8 ± 0.9 mm Hg) when measured by lumbar puncture in the left lateral recumbent position (8). In patients with INPH, the CSF-OP measured by lumbar puncture in the lateral recumbent position averages 11 ± 3.3 mm Hg (150 ± 45 mm H_2O) but may fall between 4.4 and 17.6 mm Hg (60–240 mm H_2O). The lumbar CSF-OP of INPH therefore averages slightly higher than normal but overlaps the range of pressures observed in normal subjects. This is in contrast to the acute and secondary forms of hydrocephalus, which may be associated with pressures well in excess of normal and outside the physiological range. Transient high pressures ("B waves") are detectable during prolonged intraventricular monitoring in adults with symptomatic INPH (20). CSF-OP is a poor measure of the complex temporal profile of intraventricular pressure variations that occur in hydrocephalus patients. However, the normal or modestly elevated average pressures typically observed in INPH stand in contrast to the sustained, elevated pressures commonly recorded in acute and noncommunicating forms of hydrocephalus. CSF-OP measurement may be most useful in identifying hydrocephalic conditions other than INPH, particularly when the OP is elevated above 18 mm Hg (245 mm H_2O). Expert opinion reflects that pressure elevations above this level more likely indicate secondary or noncommunicating hydrocephalus than INPH. Determination of the CSF-OP is therefore recommended when lumbar puncture or other drainage procedures are performed (which is typically performed in an effort to prognosticate about shunt responsiveness), because the CSF-OP can provide information relevant to a diagnosis of INPH.

CSF-OP in the range of 105 to 190 mm H_2O is consistent with a diagnosis of probable INPH, assuming that all other diagnostic criteria have been met. In the absence of an OP measurement or with results at the extremes of the expected range (60–104 or 191–240 mm H_2O), INPH would be considered "possible." CSF-OP outside this range makes a diagnosis of INPH unlikely. Manometric measurement of OP on lumbar puncture is the most common method for determining CSF pressure as part of the evaluation of hydrocephalus. When lumbar puncture is performed in the left lateral decubitus position, the zero point of the manometer is being positioned at the approximate height of the atrium of the heart. Before a pressure reading is made, the patient should be fully relaxed, preferably with the legs extended, for a period of 5 minutes after the spinal needle is introduced. Pulsation of the CSF column should be visible in synchrony with the heartbeat to ensure that the end of the needle is in good continuity with the subarachnoid space at the time of measurement.

Shunt-responsive and Shunt-nonresponsive INPH

Some INPH patients may be refractory to treatment and will not respond to shunting despite a diagnosis of "probable" INPH. The term *shunt-nonresponsive* (see Part III) will refer to those patients independent of diagnostic category (probable, possible, unlikely). Similarly, although it may be expected that a higher proportion of "probable" INPH patients will respond to shunting, we have applied the term "shunt-responsive" to any diagnostic category, probable, possible, or unlikely, that responds favorably to surgical intervention.

On the basis of clinical presentation alone, evidence shows that favorable response to shunting will vary from 46 to 63% (see Part III). Black (5) reported that the best indicator for shunt responsiveness was patients with the complete triad and achieved a 61.2% rate of improvement and a 35.4% complication rate. Because these data would include patients in the "probable" category, one can appreciate the value of adjunctive testing to predict shunt responsiveness. A subsequent report deals with the value of other tests beyond that of clinical presentation described here and estimates the degree of certainty of achieving a positive response to shunting. These tests include CSF lumbar tap, external lumbar drainage, or CSF resistance studies (11). We would expect that patients with "probable" INPH would have proportionally more positive adjunctive tests, if implemented, than categories of "possible and unlikely." We also posit that patients with "probable" INPH and a positive adjunctive test will have the highest percentage of favorable responses to shunting compared with the other categories.

SUMMARY AND RECOMMENDATIONS

INPH is best classified into probable, possible, and unlikely categories. It is our hope that these criteria will be widely applied in clinical practice and promote greater consistency in

patient selection in future clinical investigations involving INPH.

INPH can be difficult to diagnose accurately. Misdiagnosis and delayed recognition are two important causes of poor treatment outcome in INPH. A detailed understanding of the range of clinical manifestations of this disorder and adherence to practice guidelines should improve the timely and accurate recognition of this disorder. Familiarity with INPH and the repertoire of techniques available for its evaluation is highly desirable. In appropriate circumstances, referral to a clinician with experience and a special interest in hydrocephalus for confirmation of that diagnosis should be considered.

KEY ISSUES FOR FUTURE INVESTIGATION

The incidence and prevalence of INPH should be studied in community-dwelling, clinic, and institutionalized populations by use of standardized diagnostic criteria. The findings should be stratified according to age, sex, putative risk factors, and comorbidities.

Prospective clinical trials using the INPH classification system should provide a means of estimating the adjunct diagnostic value associated with use of new test modalities (imaging, neuropsychological, physiological, etc.) in the evaluation of INPH. Future investigations should help to establish whether prognosis for positive response to treatment is greater among patients classified as probable INPH versus possible.
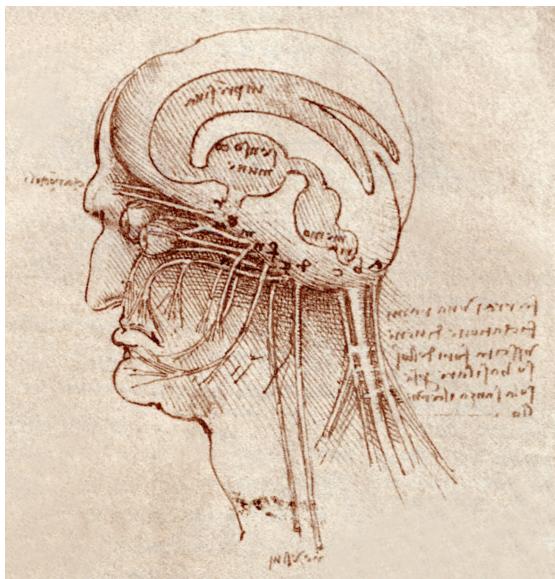
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