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AM J ALZHEIMERS DIS OTHER DEMEN 2014 29: 583 originally published online 18 February 2014
DOI: 10.1177/1533317514523485

American Journal of Alzheimer's Disease & Other Dementias®
2014, Vol. 29(7) 583-589

DOI: 10.1177/1533317514523485
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Diagnosis and Prognosis in Idiopathic Normal Pressure Hydrocephalus

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Abstract

Idiopathic normal pressure hydrocephalus (iNPH) is a communicating hydrocephalus, of unknown pathophysiology, characterized by the classical triad of dementia, urinary incontinence, and ataxia. The most popular treatment option is shunt surgery, although it is not a cure. The diagnosis of the disorder is challenging as it may mimic a lot of other neurological conditions and has no distinct biomarker. It becomes even more challenging as majority of the cases are diagnosed by invasive cerebrospinal fluid (CSF) removal tests. However, a careful history taking, a keen and detailed physical examination, and pertinent imaging studies can lead to an early diagnosis. The gait symptoms respond the most to surgery. The predictors deciding the postsurgical prognosis has been discussed. Improved shunting modalities and novel shunt materials with valve adjustments have improved the precision of the shunting procedures. Still we have lot more to achieve in terms of early diagnosis and definitive management of iNPH.

Keywords

idiopathic normal pressure hydrocephalus, imaging, biomarker, VP shunt, LP shunt, prognosis

Introduction

Normal pressure hydrocephalus (NPH) is characterized by enlarged ventricular size, with normal opening pressures on lumbar puncture along with the classic triad of dementia, gait disturbance, and urinary incontinence.[1] The disease was first described by Hakim and his colleagues in 1965.[2] The incidence of NPH varied in different studies, from 2 to 25 per million per year,[3-5] mostly owing to the inconsistent definitions used as well as demographic differences among the population sampled.

Normal pressure hydrocephalus occurs as either an idiopathic condition or secondary to a specific pathology such as subarachnoid haemorrhage or brain trauma.[1] Idiopathic NPH (iNPH) is a form of communicating hydrocephalus whose pathophysiological basis is still to be known. Per certain studies, chronic hypertension and white matter disease may lead to periventricular ischemia that increases the compliance of the ventricular wall and causes gradual ventricular enlargement.[6,7] Alternatively, periventricular ischemia may also lead to locally increased venous resistance that may lead to decreased cerebrospinal fluid (CSF) absorption and ventricular enlargement.[8] One ultrasound study conducted in patients with iNPH revealed evidence of retrograde flow in the internal jugular veins during Valsalva maneuver, suggesting an underlying incompetence of the jugular valves.[9] A recent trial studying the CSF in patients with iNPH concluded on reduced periventricular metabolism and axonal degeneration without significant cortical damage to be one of the basis of its pathophysiology.[10] Another trial suggested disturbed CSF dynamics to be one of the main culprits in iNPH and indicated reduced amplitude of cardiac-related intracranial pressure pulsations in patients benefitting from shunt surgery.[11]

Idiopathic NPH is most commonly found in adults aged more than 60 years.[12,13] The diagnosis is difficult since the presenting symptoms and the accompanying ventriculomegaly can be often attributed to aging or neurodegenerative diseases.[5] Most published guidelines advocate the role of CSF removal trials in assisting with the diagnosis,[14,15] but it does not reliably assure sustained benefit.[16] Furthermore, associated comorbidities can affect shunt response negatively.[1,16] Shunt insertion is the most widely practiced method of treatment,[17,18] with maximum improvement occurring with the gait symptoms.[5,19-21] But there is believed to be less certainty for the success of such a procedure and it has its own share of serious complications. This article tries to understand the basis of diagnosis and treatment in iNPH, the possibility of an early diagnosis, and also the predictors for the prognosis of such patients.

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Diagnosis

Clinical Differential Diagnosis

Although the clinical signs and symptoms of iNPH can be confused with that of normal aging process or other neurodegenerative diseases like Alzheimer's disease (AD) or Parkinson's disease (PD) or even vascular diseases like vascular dementia (VD), there are certain attributes in their presentation that sets them apart. In 2005, an international committee of hydrocephalus researchers published extensive "Guidelines for the Diagnosis and Management of Idiopathic NPH" to categorize patients into groups such as "probable," "possible," or "unlikely" in the decreasing chances of them having the diagnosis of iNPH.[1] For the clinical diagnosis of "probable iNPH," the age of onset was kept as more than 40 years with symptom duration of at least 3 to 6 months; for "possible iNPH," onset may begin at any age after childhood with less than 3 months of symptoms. The clinical diagnosis of "probable" requires gait or balance disturbance plus impairment in cognition or bladder control or both. Patients who present with incontinence or cognitive impairment but no observable gait or balance disturbance are categorized as "possible."

Change in the gait is the most prominent clinical feature in early stages of iNPH and is also believed to be the most responsive feature to shunting.[21] Dementia without gait disturbance can be safely excluded from the diagnosis. The gait of iNPH is described as "glued to the floor," magnetic gait, gait apraxia, or a frontal ataxia, where the steps are short, with decreased stride length and height, with outwardly rotated feet, diminished cadence, and a broadened base[22,23]—as opposed to a narrow base in PD. Patients tend to turn slowly, postural stability is impaired, and a history of falls may be reported. Occasionally, patients complain of vague aching in their legs after walking a moderate distance. The American Academy of Neurology has found level B support for the use of clinical gait assessment tests such as Tinetti Assessment Tool or Timed Up and Go test for patients with iNPH.[24] A computerized analysis of the gait reveals an abnormal tendency toward contraction in antagonist muscle groups, along with decreased rotation in the pelvis and counterrotation of the torso, indicating a deficit in subcortical motor control.[22] Functional neuroimaging studies suggest a disorder in the supplementary motor areas in the frontal lobe.[25]

The cognitive disturbance of NPH has prominent subcortical and frontal features with psychomotor slowing, decreased attention and concentration, and apathy, unlike other forms of dementia like VD. Vascular dementia is a more likely diagnosis when there is a stepwise history of cognitive deterioration with asymmetric signs. Lack of delusion or visual hallucinations or presence of nonfluctuating cognitive status distinguishes NPH from Lewy-body dementia. Cortical features (aphasia, agnosia, and apraxia) are less prominent in NPH compared to VD or AD. Executive function is impaired early in the course of NPH and may be more resistant to treatment.[26] In the late stages, there are frontal release signs, such as akinesis, mutism, and quadriparesis. The iNPH can be differentiated from frontotemporal dementia (FTD) by a lack of personality change, impulsiveness, or aphasia. The iNPH may also coexist with other dementias, particularly AD.[5,27-29] In studies of patients with NPH, biopsies carried out at the time of shunting reveal AD pathology.[19,28-32] Two series have found that the degree of AD pathology correlated with the degree of cognitive impairment.[29,30] Urinary urgency may be present early in iNPH, which may turn to urinary incontinence in later stages.

Imaging

Per the published guidelines,[1] for "probable iNPH," imaging studies must show "ventricular enlargement not entirely because of cerebral atrophy or congenital enlargement" with an Evans index (the ratio of the maximal diameter of the frontal horns of the lateral ventricles to the maximum width of the cranial cavity measured at the inner tables of the skull) greater than 0.31, "no macroscopic obstruction to CSF flow," and at least one additional supporting feature. Acceptable supporting features include "enlargement of the temporal horns not entirely attributable to hippocampal atrophy," "callosal angle of 40° or greater," "periventricular signal changes not attributable to microvascular ischemia or demyelination," or "aqueductal or fourth ventricular flow void." To receive a diagnosis of "possible iNPH," the ventriculomegaly may be associated with severe atrophy, and imaging need not demonstrate any supporting factors.

Magnetic resonance imaging (MRI) is a more reliable diagnostic procedure than computed tomography (CT) as it permits better visualization of the posterior fossa, allows volumetric assessment, and is more sensitive in diagnosing an associated cerebrovascular disease. In NPH, MRI may show a characteristic high-signal abnormality around the ventricles, which is thought to represent transependymal egress of fluid. The extent of white matter disease may correlate with the degree of cognitive impairment.[26] Diffusion-weighted imaging (DWI) may help distinguish between chronic ischemic changes and the white matter changes associated with NPH.[33] Increased diffusivity is noted in the former condition, while patients with NPH had similar diffusivity compared with controls. The DWI studies have also distinguished iNPH from PD—where it had significant lower fractional anisotropy for anterior thalamic radiation and forceps minor.[34]

Neuropsychological Testing

Neuropsychological (NP) testing in iNPH holds limited value, although it may help to distinguish it from VD, AD, or FTD as discussed earlier. The characteristic pattern of NP testing is that of "frontal–subcortical" dysfunction in which the patient is slower in timed tasks, performs poorly on tests of divided attention and executive function, has difficulty with fluency tests, and has poor learning and better preserved recognition memory.[26,35] The NP test results may serve as a baseline measurement for future comparison after a diagnostic or surgical

procedure and may also aid in prognosis. The presence of anomia has been associated with a lesser benefit from surgery.[36] Recent multicenter study in Europe found Rey Auditory Verbal Learning Test to be the most sensitive for diagnosing the cognitive deficits of iNPH, and the Grooved Pegboard and the Stroop test to be more sensitive to selecting candidates for shunting.[37] A new scale called the iNPH scale has been recently developed, which assesses all the 4 domains involved—gait, neuropsychology, balance, and continence.[38]

Cerebrospinal Fluid Biomarkers

Till the recent past, no reliable CSF biomarker to diagnose iNPH or predict its outcome postshunt surgery has been found.[39,40] A recent observational study has revealed that patients with iNPH who got improved by surgery show a greater increase in amyloid precursor protein (APP)-derived proteins in CSF following shunting than did those who did not improve.[10] But this study did not consider the level of the biomarker preoperatively. However, another recent trial has observed soluble APP-α to be a suitable biomarker for the differentiating patients with iNPH from patients with AD and also picture their prognosis to shunt surgery.[41] Nevertheless, we need more such studies focused on establishing a biomarker to predict the postshunt prognosis in patients with iNPH before reaching any conclusion.

Cerebrospinal Fluid Removal

Cerebrospinal fluid tap test (Fisher test). This is an outpatient procedure and 30 to 50 mL of CSF is removed via lumbar puncture, with documentation of the patient's gait and cognitive function before and 2 to 3 hours after the procedure. It has an accuracy of 53%.[42] Documented improvement in one or more of these measures may suggest that the patients will have a better outcome after placement of a ventriculoperitoneal (VP) shunt.[43] This test has excellent positive predictive value (90%-100%) but limited negative predictive value (18%-50%); hence, a significant number of patients who show no response to removal of CSF later improve with surgery.[42,44-46]

Lumbar drainage. This is an inpatient procedure involving continuous CSF drainage at a rate of 5 to 10 mL/h via a temporary catheter in the lumbar CSF space and the clinical response is observed over 2 to 7 days. In a small series, this technique has reportedly had 100% sensitivity and specificity in predicting subsequent response to shunting.[47,48] Prolonged lumbar drainage may cause meningitis and subdural hematoma.[45,49]

Treatment

Conservative

Acetazolamide and osmotic diuretics are sometimes used in patients with iNPH. Memantine has shown some positive effects on those with neuropsychiatric symptoms.[50] But prospective cohort studies comparing surgical to conservative treatment in patients with iNPH have revealed moderate to marked improvement in cognition, balance, urinary functioning, or activities of daily living in most of the shunted population, while majority of the unshunted patients either had marked worsening of symptoms or had no change from their baseline levels.[51-55]

Surgical

Shunting is the standard of surgical care for iNPH. The VP shunts are the most popular, while the ventriculoatrial (VA) shunts are rarely implanted because of their more frequent long-term complications.[56] Lumboperitoneal (LP) shunts too are being increasingly tried.[57] Gait impairment as stated earlier is the symptom that is most responsive to shunting[5,19-21]; cognitive impairment may improve with surgery if it is not very severe at the time of intervention[21,26,44,58] while urinary incontinence improves in 36% to 90% of patients.[5,20,44,59,60]

Ventriculoperitoneal shunting. Ventriculoperitoneal shunts are surgically placed inside one of the brain's ventricles to divert fluid away from the brain into the peritoneal cavity in order to restore normal CSF dymanics: more research is needed toward understanding the pathophysiology of iNPH and the mechanism behind the individual shunts. These shunts are attached with a valve for CSF flow regulation. The current evidences favor the use of adjustable shunt valves in the treatment of iNPH.[61,62] The option of adjusting the valves' opening pressure noninvasively enables fine-tuning of the ventricular drainage. Unlike the older valves, new generation valves can withstand automatic reprogramming in magnetic fields of up to 3 T.[63]

A low valve opening pressure at the supine position is an important factor in therapeutic success in iNPH.[62] Such a low pressure, however, may be associated with a high risk of overdrainage in a mobile patient. The commonest ones used in regular practice is differential pressure regulated valves that work on the basis of the difference in hydrostatic pressure between proximal catheter tip in the ventricles and distal catheter tip in the abdomen, pleura, or atrium; but in upright position, it causes "siphoning" and overdrainage. Differential flow-regulated valves flow independent of patient positioning, but it is associated with underdrainage. Hence, another class of useful valves, called gravity controlled valves (G valves), was introduced. The opening pressure in G valves is mainly controlled by gravity: they present a lower resistance to CSF flow when horizontal than when vertical and hence lowers the risk of overdrainage by 90% in mobile patients with iNPH, without impairing the efficacy of treatment.[64]

There were high incidence of shunt-related complications with VP shunts in the past, such as failure, infection, obstruction, over-/underdrainage, or subdural hematoma; but with the advent of advanced materials for shunt and newer valves, the complications have also fallen to less than 20%.[63-66] Complications unrelated to shunting, such as seizures and intracerebral hemorrhage, have also significantly lowered in recent times.[64]

Lumboperitoneal shunting. Lumboperitoneal shunting is a less commonly used technique of CSF diversion from the lumbar thecal sac to the peritoneal cavity. It can be equally effective as VP shunts for the treatment of iNPH.[57] It has the advantage of being a completely extracranial procedure and less risk of intracranial complications. Some studies have illustrated lower incidences of infection,[67] malfunction,[67] or Arnold Chiari Malformation[67,68] with a LP shunt than with a VP shunt. Placement of LP shunts with a horizontal–vertical valve is an even safer procedure, and it prevents overdrainage and its complications such as subdural hematoma.[57,69] More clinical trials establishing its potential may be required before its routine use in patient care.

Follow-Up and Predictors of Prognosis

Two to three postoperative follow-up visits are advisable in the first year after shunting, the period when most complications tend to arise.[70] Patients with an uncomplicated course can be followed up thereafter at 1 to 3 years, while patients who have had shunt failures and infections in the past should be followed up more often. Aside from the physical examinations, cerebral imaging should be performed at some point during the first year after shunting and a few weeks after any resetting of the opening pressure of adjustable valves. Patients with VA shunts should have regular testing of their C-reactive protein concentration[56,71] and D-dimers[64] for the early detection of subclinical chronic septicemia or thromboembolism. In the past, a marked reduction in ventriculomegaly was considered to be a postsurgical sign of adequate drainage. After G valves were introduced, it was evident that such a dramatic narrowing of the ventricles is unnecessary and is rather an expression of overdrainage.[62,66] With a G valve, the ventricles may become only a little bit narrower despite therapeutically adequate drainage. The only reliable sign of adequate drainage in a CT or MRI is a freer subarachnoid space in the vicinity of the vertex-near cisterns compared to the preoperative image.[64]

Patients treated early in their course of NPH may live for more than 5 years.[72,73] Patients with iNPH showed lower rates of improvement after shunt placement than patients with NPH with a known etiology[19,44,58,74]; however, the current guidelines refuse to compare the 2 groups.[1] Patients with symptoms of less than 6 months of duration have the highest chance of improvement, compared to those with symptoms, particularly dementia, for more than 2 or 3 years.[12,36,49,75] Those with moderate to severe dementia are unlikely to improve after shunting.[43] This may reflect progression of NPH to an advanced stage in which neurologic injury is fixed or that an underlying degenerative dementia such as AD is the cause or contributor to patient's symptoms.[20,30] Most studies do not find that age influences surgical outcome.[19] However, in one series, advanced age predicted a worse response to temporary lumbar drainage.[46] Late appearance of gait symptoms or no gait disorder predicts a poor surgical outcome in more than 80% of patients compared to those with early gait disorder.[43,76,77] Evidence of marked white matter disease in the initial imaging also leads to worse long-term outcomes.[78,79] Presence of other acute comorbidities also affect the prognosis postshunt surgery.

Conclusion

Over the years, iNPH has emerged more as a "treatable gait disorder" than a "treatable dementia." Its pathophysiology is still unknown, and more credible research studies are needed in that direction. The commonest treatment modality is shunt surgery although there is not yet any definitive cure. Patients with iNPH can mimic an array of neurological disorders, but a careful history taking, a keen and detailed physical examination, and pertinent imaging studies like DWI in suspected patients can lead to an early diagnosis. The CSF removal tests like Fisher test and lumbar drainage aid in predicting patients who may benefit from shunt surgery, although it can't predict who are not a good candidate for surgery. Detection of the disease in early stages also ensures a better prognosis postshunting. We need some reliable biomarker that can predict the outcome postsurgical intervention. Patients with associated degenerating conditions are less likely to get benefit from the surgical procedures and need concomitant treatment of their respective comorbidities. There is also a lot of ongoing research on the various shunting modalities and advent of improved shunt materials, and valve adjustments have improved the precision and reduced the morbidity and mortality associated with the shunting procedures. Hence, iNPH has slowly evolved as a curable syndrome.

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

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