


Idiopathic Normal Pressure Hydrocephalus: A Review for General Practitioners

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Abstract

Idiopathic normal pressure hydrocephalus (iNPH) is a potentially reversible neurodegenerative disease commonly characterized by a triad of dementia, gait, and urinary disturbance. Advancements in diagnosis and treatment have aided in properly identifying and improving symptoms in patients. However, a large proportion of iNPH patients remain either undiagnosed or misdiagnosed. Using PubMed search engine of keywords “normal pressure hydrocephalus,” “diagnosis,” “shunt treatment,” “biomarkers,” “gait disturbances,” “cognitive function,” “neuropsychology,” “imaging,” and “pathogenesis,” articles were obtained for this review. The majority of the articles were retrieved from the past 10 years. The purpose of this review article is to aid general practitioners in further understanding current findings on the pathogenesis, diagnosis, and treatment of iNPH.

Keywords

normal pressure hydrocephalus, diagnosis, treatment

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Introduction

The term *hydrocephalus* is used to describe excess accumulation of fluid within the brain. Typically hydrocephalus is separated into two categories: obstructive and communicating. Obstructive hydrocephalus requires a physical blockage within the cerebrospinal fluid (CSF) flow pathway that results in proximal but not distal hydrocephalus. Communicating hydrocephalus is in contrast a defect in reabsorption of CSF. Normal pressure hydrocephalus is a form of communicating hydrocephalus. The term was first coined by Adams, Fisher, Hakim, Ojemann, & Sweet, 1965 to describe hydrocephalus with enlargement of ventricles, normal CSF pressure, and a triad of symptoms: gait disturbance, dementia, and urinary incontinence (Adams et al., 1965). Primary or idiopathic normal pressure hydrocephalus (iNPH) can be distinguished from secondary by causation; meningitis, trauma, are subarachnoid hemorrhage are inducers of secondary NPH. Most cases of NPH are idiopathic. Presently, NPH is one of the only reversible forms of dementia. The prevalence rate varies from .3% up to 3% in patients greater than 65 years old (Hiraoka, Meguro, & Mori, 2008; Jaraj et al., 2014; Rosell et al., 2015). The number of patients thought to have NPH is likely greater than documented. This can be attributed to similarities between NPH and other neurodegenerative diseases, making it difficult to diagnose. Currently, the

only effective treatment for NPH is shunt surgery. This review is intended for general physicians to highlight the pathophysiology of idiopathic NPH, diagnosis, treatment, and new findings within the past 10 years.

Pathophysiology

The pathophysiology of idiopathic NPH remains controversial and not well elucidated. Many theories have been suggested, the most prominent being disturbances in CSF dynamics and resistance, brain parenchyma alterations, and vascular abnormalities. The route of CSF is postulated to begin with production from the choroid plexus to flow through the ventricles, cisterns, and subarachnoid space ending with reabsorption within the arachnoid villi. Flow of CSF was thought to be dependent on the ratio of CSF absorption and production, termed the bulk flow theory. This is only one component of CSF dynamics, the other being pulsatile flow through the Virchow–Robin spaces, surrounding arterioles and venules coursing from the subarachnoid space through brain parenchyma (Brinker, Stopa, Morrison, & Klinge,

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Table 1. iNPH Versus Parkinson's Disease Gait Characteristics.

	iNPH	Parkinson's disease
Gait	Magnetic (stuck on floor appearance) Broad based steps with short strides March a petits pas (short steps with upright stance)	Flat foot strike Rapid shuffling with short strides Festinating (short steps with flexed forward postural stance)
Arm swing	Preserved, normal swing	Decreased, asymmetrical swing
Turns	Start and turn hesitation	Start and turn hesitation with en bloc turns (rigid neck and trunk)
Foot position	Increased foot rotation/outward angle	Normal

Source: Bugalho, Alves, and Miguel (2013); Bugalho and Guimaraes (2007); Grabli et al. (2012); Salzman (2010).

Note. iNPH = Idiopathic normal pressure hydrocephalus.

2014). The latter is influenced by cardiac pulse pressure (Greitz, 1993).

According to Hakim and Adam's hypothesis, NPH occurs when CSF absorption is decreased resulting in increased intracranial pressure. Over time, ventricular enlargement occurs as a compensatory mechanism. This results in a new intracranial pressure steady state (Adams et al., 1965). As a modification, CSF flow is directed more toward the Virchow–Robin spaces into brain parenchyma. Parenchymal changes occur resulting in tissue compression and deep white matter ischemia, hallmarked by myelin pallor. Periventricular damage results in reduced cellular metabolism and clearance of toxins. A marker of neuronal damage, myelin basic protein, has been shown to be elevated in iNPH patients (Pyykkö et al., 2014). Recent studies have explored glucose metabolism in iNPH. Results showed global impairment of metabolism correctable within 1 week of shunt treatment (Calcagni et al., 2013). In addition, the coexistence of Alzheimer's disease in iNPH patients has been documented and shown to be of increased prevalence. This can be partially attributed to decreased neurotoxin clearance, specifically amyloid B protein and microtubular associated protein (Silverberg, Mayo, Saul, Rubenstein, & McGuire, 2003). Global brain stiffness, decreased strength, and elasticity, via magnetic resonance enterography studies, have been documented in iNPH with a renormalization of parenchymal topography in shunted individuals (Friemann et al., 2012).

Multiple studies have examined the role of cerebral perfusion in iNPH. Certain studies have demonstrated decreased blood flow in periventricular white matter, temporal lobe, frontal lobe, thalamus, and basal ganglia. Within these studies, correlations of clinical improvement and increased cerebral blood flow (CBF) have been examined. A recent study by Virhammar et al. found an improvement in gait and balance dysfunction among NPH individuals after CSF tap testing due to increased CBF in the frontal and lateral lobes (Virhammar, Laurell, Ahlgren, Cesarini, & Larsson, 2014). Another study using $[^{15}O]H_2O$ uptake found that patients with clinical improvement post shunt treatment showed increased uptake within the frontal cortex (P. M.

Klinge et al., 2008). Using positron emission tomography (PET) scans, Owler et al. (2004) identified significant decrease in CBF within the cerebrum, cerebellum, and deep gray matter regions—thalamus, putamen, and caudate nucleus—in iNPH patients as compared with healthy individuals. In addition, venous compliance in iNPH is found to be reduced by up to 50%, particularly in the sagittal sinus (Bateman, 2008).

Diagnosis

In 2012, the second edition of the international Japanese guidelines for normal pressure hydrocephalus was published, outlining diagnostic criteria. There is a degree of interlace between clinical symptoms of iNPH and other neurodegenerative conditions, making it harder to clinically differentiate. Thus, a mixture of clinical, neuropsychological, and diagnostic imaging is key to establishing diagnosis.

Clinical Manifestations

The most prominent characteristics of iNPH are gait, cognitive, and urinary dysfunction. This triad develops insidiously, usually beginning with symmetrical gait dysfunction characterized by broad based, small stepped instability and difficulty initiating movements. A known scale employed to objectify iNPH gait symptoms is the Gait scale developed within the Dutch normal pressure hydrocephalus study. Other general gait tests utilized include Berg Balance Scale, Functional Reach Test, and Timed Up and Go Test. In particular, gait dysfunction in iNPH is difficult to distinguish from Parkinson's disease. Both are hypokinetic with reduced postural responses (Table 1). A comparative study by Bugalho, Alves, and Miguel (2013) found subtle differences in movement, mainly iNPH has more frontal gait dysfunction—disequilibrium, abnormal stance, postural adjustments. Frontal lobe executive dysfunction and psychomotor slowing leads to dementia. Urinary dysfunction results from detrusor muscle overactivity. Urgency, nocturnal, and diurnal frequency are usually present, along with awareness of symptoms (Sakabkibara et al., 2007). It should be noted that only 60% of patients

present with this triad. Lesser symptoms include apathy, anxiety, and aberrant motor activity (Kito et al., 2009).

Neuropsychological Testing

Neuropsychological deficits are known in patients with iNPH. The degree of severity of iNPH symptoms prominently gait, urinary urgency, and sleep disturbances have been shown to correlate with test performance. Comorbidities such as diabetes and cardiovascular disease are also linked with poorer performances (Hellstrom et al., 2007). The use of neuropsychological testing is by no means definitive in detecting iNPH. However, it can be used to shed light on minor distinctions between iNPH and other cognitive disorders. Testing of cognition, attention, executive function, language, and memory, Saito et al.'s (2011) comparison of iNPH and Alzheimer's disease revealed that iNPH is associated more with executive frontal lobe and attention deficits than with memory impairment, as seen in Alzheimer's. Furthermore, Saito et al. contrasted visuospatial and visuospatial deficits of both groups and found a higher degree of impairment among iNPH patients. Earlier studies by Ogino et al. had also identified worsened attention/concentration and psychomotor slowing with better memory and short-term recall functions in iNPH as compared with Alzheimer's patients (Ogino et al., 2006).

A major role for neuropsychological testing within iNPH is detecting clinical improvement pre and postoperative shunting. Studies have shown improvement of cognitive functioning post shunt (Duinkerke, Williams, Rigamonti, & Hillis, 2004; Hellstrom et al., 2008; Katzen et al., 2011; Thomas et al., 2005). An interesting question is whether a specific set of tests can be structured to optimally detect iNPH and improvements post shunt. Common tests employed in studies include the Stroop test, Ray auditory verbal learning test (RAVLT), Digit span, Rey Osterrieth complex finger test, and Trail making test A and B.

Moreover, the extensive process of neuropsychological testing is difficult for many iNPH patients. Consequently, there should be a construct of brief bedside cognitive tests for clinicians, especially those with nonimmediate access to neuropsychologists. A minimal status exam should be performed in iNPH candidates; however, it does not effectively test for executive dysfunction. More sensitive tests to utilize include the Montreal Cognitive Assessment (MoCA) or Addenbrooke's cognitive examination (Dong et al., 2012; Velayudhan et al., 2014). The Executive Interview (EXIT 25) is a 25-item test that focuses on executive dysfunction and may be useful in iNPH. A novel counting-backward test, created by Satio et al. for recognizing executive dysfunction, has also shown to be effective in distinguishing iNPH and Alzheimer's disease patients (Kanno et al., 2012).

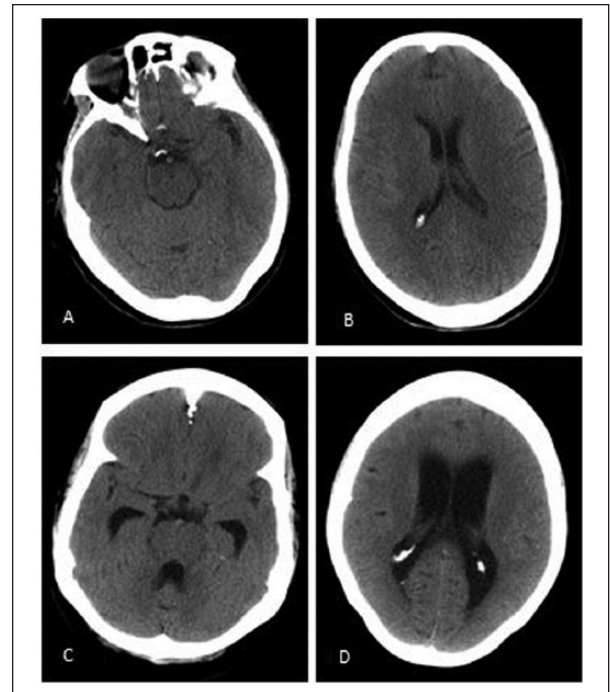


Figure 1. A and B: CT scan of a 71-year-old female with normal cognitive function showing normal ventricular size; C and D: CT scan of a 68-year-old female with iNPH showing enlarged ventricles at the level of the parietal and temporal lobes.

Note. Images B and D show normal sized gyri and sulci. CT = computed tomography; iNPH = Idiopathic normal pressure hydrocephalus.

Imaging

If suspicion of iNPH occurs, imaging by either computed tomography (CT) or magnetic resonance imaging (MRI) should be performed. Evidence must show ventricular enlargement without signs of CSF obstruction or significant sulcal enlargement. As ventricular enlargement occurs with other dementias and to an extent normal aging, a ratio of maximum width of the frontal horns of the lateral ventricles and the maximal internal diameter of the skull, known as the Evans index, of $>.3$ correlates with iNPH (Figure 1). This index is only a rough marker for ventriculomegaly, and thus, there has been recent debate of its accuracy and reliability in iNPH diagnosis (Toma, Holl, Kitchen, & Watkins, 2011). Lateral enlargement within the temporal and frontal horns can also be present in iNPH. Some studies have suggested a disproportionate enlargement of the subarachnoid space (DESH) as a marker for iNPH, along with dilation of the Sylvian fissure (Virhammar, Laurell, Cesarini, & Larsson, 2014). Another diagnostic marker used is a callosal angle >40 , the angle measured between the lateral ventricles on coronal fields. The callosal angle should be steep due to the elevation of the dilated lateral ventricles. In a study by Ishii et al., a callosal angle <90 is a rough cutoff of differentiating iNPH from Alzheimer's disease (Ishii et al., 2008). The presence of

aqueductal flow void and periventricular signal changes not attributable to microvascular ischemic changes are also suggestive of iNPH. In iNPH, there is an increased CSF flow velocity observed that leads to loss of signaling on imaging in the aqueduct of Sylvian. Absence of flow void does not exclude iNPH given other findings. A recent study used diffusion tensor imaging to differentiate between white matter changes in NPH versus Alzheimer's (Horinek et al., 2016).

Biomarkers

To date, there is no established role in the use of biomarkers for diagnosing iNPH. Several studies have looked at the role of pro-inflammatory cytokines in iNPH with mixed results (Leinonen et al., 2011). Others have tried to differentiate differences in tau and AB subtypes between iNPH and Alzheimer's but currently there is no conclusive evidence to support utilization of these markers (Pyykkö et al., 2014; Tsai, Malek-Ahmadi, Kahlon, & Sabbagh, 2014).

Treatment

Shunting

Ventriculoperitoneal shunting is the mainstream treatment for iNPH. Success rates are variable, from 50% to 80% (P. Klinge, Marmarou, Bergsneider, Reklun, & Black, 2005; Shprecher, Schwalb, & Kurlan, 2008). A shunt is inserted with a proximal and distal catheter, into ventricular or lumbar subarachnoid space and the peritoneal cavity, respectively. In between, there is a valve that opens in response to the changes in pressure between the catheters. That change in pressure varies from the supine to upright position and hence an important factor in determining the effectiveness of a shunt. The two types of valve shunt systems used to treat NPH are gravitational and programmable. Gravitational valves open in response to the amount of fluid present, whereas programmable valves require a set pressure point to open. If programmable valve pressure is not correctly adjusted for, possible overdrainage or underdrainage can occur leading to subdural hematomas or ineffective shunting. The Shunt Valves plus shunt Assistant versus Shunt valves alone for controlling Overdrainage in idiopathic Normal pressure hydrocephalus in Adults (SVASONA) trial compared the efficacy of gravitational versus programmable valves. Findings suggested that gravitational valves may be a better option for iNPH patients due to reduction in overdrainage of CSF (Lemcke et al., 2013).

An alternative to ventriculoperitoneal shunting is lumboperitoneal shunting. The latter has been underutilized by neurosurgeons due to increased prevalence of higher malfunctioning rates, shunt blockage, radiculopathy, and infection (Wang et al., 2007; Yadav, Parihar, & Sinha, 2010). In contrast, the benefit of using a lumboperitoneal shunt is avoiding an invasive intracranial procedure. This

potentially reduces the risk of subdural hematoma, associated with ventriculoperitoneal shunts (Bloch & McDermott, 2012). The 2015 Study of Idiopathic Normal Pressure on Neurological Improvement-2 (SINPHONI-2) trial, led by Kazui, examined the effectiveness of lumboperitoneal shunt surgery in an immediate group and a conservative group (surgery was postponed 3 months as patients were instead performing physical exercises). Results illustrated improvement in overall functional status at 3 and 12 months post surgery with the most common adverse effect being postural headache and most serious being cerebral infarct and, later correctable, shunt malfunction/placement issues (Kazui, Miyajima, Mori, & Ishikawa, 2015).

Prognostic Indicators

The prognostic value of shunt surgery in iNPH is dependent on accurate diagnosis. Patients diagnosed at an early age (<70) have been thought to have better shunt response. Comorbidities, specifically cardiovascular disease, and longer disease duration increase the likelihood of poorer shunt response. Clinically, patients presenting with early or severe dementia have worse outcome, while those with a primary gait disturbance feature have better results (Bugalho et al., 2013; Poca et al., 2005).

Certain MRI characteristics as mentioned above can help identify iNPH patients. Recently, Virhammar et al. explored the preoperative prognostic MRI findings in iNPH. They concluded the following: Patients with normal sylvian fissures, without periventricular hyperintensities, small callosal angles, disproportionate enlargement of subarachnoid space, and wide temporal horns are likely to have a positive shunt response (Toma et al., 2011). Other studies have studied the prognostic power of CSF flow dynamics. Some results indicate that higher, increasing stroke volume with progression of disease can indicate positive response to shunting. While decreasing stroke volume over time can predict irreversible damage and shunt unresponsiveness (Scollato et al., 2009).

Once MRI findings are suggestive of iNPH, CSF tap test can indicate shunt outcome. Clinical improvement after 30 to 60 ml of fluid removal is generally a positive predictor of shunting (Verrees & Selman, 2004). However, a lack of improvement in CSF tap testing does not indicate negative shunt response. External lumbar drainage, for 72 hr, is then indicated and is a better predictor of treatment (Marmarou et al., 2005).

Conclusion

In conclusion, iNPH remains a hotly discussed and researched disease because of its role in being a treatable neurocognitive condition. Focus should continue to be on efficiently and effectively diagnosing and treating iNPH patients. As of now, diagnosis is difficult because

iNPH symptoms are similar to other neurocognitive diseases. To distinguish the difference, excellent clinical skills and diagnostic/imaging modalities are required. Although treatment with shunting has been cemented in practice, shunting protocols and preoperative evaluation of candidates are worthy of attention.

Declaration of Conflicting Interests

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