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Current research of idiopathic normal pressure hydrocephalus: pathogenesis, diagnosis and treatment

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Abstract

Idiopathic normal pressure hydrocephalus (iNPH) is caused by impaired cerebrospinal fluid absorption in the elderly; it is a surgically treatable form of dementia. Gait disturbance, dementia, and urinary incontinence are the triad of signs for iNPH. In addition to these clinical findings, imaging studies show characteristic ventricular enlargement. High Evans Index and 'disproportionately enlarged subarachnoid hydrocephalus' are other well-known imaging findings of iNPH. If the tap test shows improved symptoms, shunt surgery is performed. The disease was first described by Hakim and Adams in 1965, followed by the publication of the first, second, and third editions of the guidelines in 2004, 2012, and 2020, respectively. Recent studies signal the glymphatic system and CSF absorption from the dural lymphatics as aetiological mechanisms of CSF retention. Research is also underway on imaging test and biomarker developments for more precise diagnosis, shunting technique options with fewer sequelae and complications, and the influence of genetics. Particularly, the newly introduced 'suspected iNPH' in the third edition of the guidelines may be useful for earlier diagnosis. However, less well-studied areas remain, such as pharmacotherapy in non-operative indications and neurological findings other than the triadic signs. This review briefly presents previous research on these and future issues.

INTRODUCTION

Idiopathic normal pressure hydrocephalus (iNPH) was first reported by Hakim and Adams^[1] in 1965. In 2004, the first global guidelines for iNPH were published^[2]. The guidelines placed the tap test at the centre of the diagnostic algorithm. A second edition of the guidelines was published in 2008^[3]. These guidelines emphasised the importance of clinical features such as gait disturbance, urinary incontinence, and cognitive impairment, as well as 'disproportionately enlarged subarachnoid hydrocephalus' (DESH).

PATHOPHYSIOLOGY

Classically, the third circulation theory (bulk flow theory) has been considered the established theory for CSF production and absorption. In this theory, CSF is produced from blood in the choroid plexus within the ventricles, and the CSF has a steady flow. CSF flows from the uppermost lateral ventricles and drains through the foramen of Monroe, the third ventricle, the middle cerebral aqueduct, and the fourth ventricle, into the subarachnoid space. In the subarachnoid space, CSF further flows from the posterior cranial fossa through the basilar, sylvian, and cerebral hemispheric fissures to the higher arcuate region in the vicinity of the superior sagittal arteriovenous system. However, more recently, involvement of the glymphatic system and a mechanism of CSF absorption from the dural lymphatics has been considered more appropriate^[4,5]. According to these theories, CSF is produced from the interstitial fluid produced by brain cells via the glymphatic system. Some CSF drains into the ventricles and has a steady flow, as in the classical theory. However, the majority of CSF is absorbed from the intradural lymphatics by anomalous flow. Future research is needed on the relationship between these new theories and clinical ventricular enlargement mechanisms.

GENETICS

Future research is needed to identify the relationship between these new theories and clinical ventricular enlargement mechanisms. iNPH has been classified as secondary hydrocephalus, with it being secondary to subarachnoid haemorrhage and other conditions, and the actual cause of iNPH may be unknown. Although there have been reports of sibling cases, there are no reports of familial or hereditary hydrocephalus. However, familial normal pressure hydrocephalus (fNPH) has recently been reported, with affected families being reported from Japan in 2011^[6], Canada in 2012^[7], and Greece in 2014^[8]. There is also a family history of shunting in 5% of patients with iNPH in Finland^[9]. Thus, fNPH may exist in clinically important numbers. In addition, the gene encoding the protein 'Scm-like with four MBT domains protein1 (SFMBT1)' has been reported as a risk gene for iNPH, and the cilia-and flagella-associated protein 43 (CFAP43) as a causative gene for fNPH in the field of genetic medicine^[10,11]. SFMBT1 localises to cells constituting the subarachnoid space, cerebral arteries, veins, and ventricular walls. CFAP43 affects proteins related to villus structure and function. Therefore, research on fNPH may also help in understanding the pathogenesis of iNPH and developing treatment.

KEY POINTS OF THE THIRD EDITION OF THE GUIDELINES

Traditionally, the diagnosis of iNPH was classified into three levels: possible, probable, and definite. However, "suspected iNPH" was added in the third edition of the guidelines. Suspected iNPH is defined by two conditions: 1) an age of 60 years or older, and 2) enlarged ventricles (Evans Index > 0.3) on head imaging. Clinical symptoms such as dementia, gait disturbance, and dysuria are not required. This classification is expected to lead to earlier diagnosis of iNPH and earlier treatment^[12]. In the study of asymptomatic iNPH, there is also the concept of asymptomatic ventriculomegaly with features of iNPH on MRI (AVIM)^[13]. AVIM describes the additional finding of ² narrowing of the subarachnoid space and cortical sulci at the high convexity of the cerebrum to the classification of suspected iNPH. AVIM may also represent a preclinical stage of iNPH.

IMAGING

In the diagnosis of iNPH, head imaging findings are as important as abnormal neurological findings such as dementia, gait disturbance, and dysuria. It should be noted that ¹imaging findings alone should not rule out iNPH. Diffusion tensor imaging (DTI), single photon emission computed tomography (SPECT), and FDG-PET imaging are also useful in the diagnosis of iNPH. However, they are omitted from this discussion owing to word count limitations.

¹*Differentiating iNPH from Alzheimer's disease*

When making the diagnosis, it is important to differentiate between Alzheimer's dementia and iNPH, but in real-life practice this is often difficult. Indeed, in Europe and Japan, iNPH is considered as an independent disease, whereas in the United States it is classified as a subtype of Alzheimer's disease^[14].

zEI and BVR 200

¹In iNPH, the Evans Index is usually > 0.3 (Figure 1). The subarachnoid space is often enlarged in the sylvian fissure and downwards, with stenosis in the high arc region^[15-18]. DESH is also an important imaging finding, as discussed in 'Changes in iNPH guidelines' (Figure 2). DESH and cerebral atrophy due to Alzheimer's disease can be differentiated with high sensitivity and specificity^[16-18]. DESH can be assessed visually, but previous studies have examined atrophic changes in more detail using voxel-based morphometry (VBM)^[18]. In addition to DESH, other evaluation criteria of interest include the Z-Evans Index (zEI) and brain/ventricle ratio (BVR) (Figure 3). The (classic) Evans Index is a useful indicator of lateral ventricular enlargement in the horizontal section direction. However, in practice, iNPH patients often have lateral ventricles that show high-convexity tightness visible in the z-axis rather than in the horizontal section. The zEI is defined as the maximum z-axis length of the cranium from the maximum z-axis length of the frontal horn. This index is useful for detecting ventricular

enlargement in the z-axis direction rather than in the horizontal sectional direction^[19]. Yamada suggested that zEI may be associated with tap-test positivity. BVR is defined as the width of the anterior horn of the lateral ventricle/intracranial width immediately above the lateral ventricle^[20]. A BVR < 1.0 in coronal sections on anterior commissure points, or a BVR < 1.5 in coronal sections on posterior commissure points, is considered an indicator of DESH findings^[20].

Rad scale

The radiological scale (Rad scale) has a total score of 12 points and is used to assess iNPH over the following seven items: 1) widening of the ventricular/intracranial cavity width ratio (Evans Index > 3.0), 2) widening of the sylvian fissure, 3) narrowing of the high circumflex and median subarachnoid space, 4) steepening of the cerebral corpuscle angle, 5) focal widening of the cerebral sulci (a pooling phenomenon of cerebrospinal fluid), 6) widening of the lateral subventricular angle, and 7) periventricular hyperintensity (PVH) (Figure 4)^[21]. The Rad scale correlates with the severity of iNPH^[22]. The Rad scale is also useful for distinguishing subjects with iNPH from healthy elderly people, and for the differential diagnosis between iNPH and cerebrovascular dementia, progressive supranuclear palsy, and multiple system atrophy^[23].

BIOMARKERS

Proteins and neuropeptides in cerebrospinal fluid have been studied as biomarkers for iNPH. Previous studies reported comparisons of total tau, phosphorylated tau, and amyloid- β 42 between iNPH and Alzheimer's disease^[24-31]. In addition, leucine-rich α 2-glycoprotein (LRG), protein tyrosine phosphatase receptor type Q (PTPRQ), and neurofilament light chain (NfL) are biomarkers that have recently received attention^[32-34]. These are useful markers not only for diagnosis, but also for predicting the effect of shunting. In iNPH, total tau and phosphorylated tau are generally lower than in Alzheimer's disease, with higher levels predicting a poor response to shunting.

Amyloid- β 42 is also lower in patients with iNPH than in healthy subjects, and low levels are an indicator of a poor response to shunting procedures. NfL-PTPRQ-LRG is higher in patients with iNPH than in healthy subjects. High NfL-LRG values are indicative of poor effectiveness of shunting procedures, but the relevance of high PTPRQ is unknown. Future work in this area is likely to focus on whether these biomarkers can be combined to make them more sensitive for diagnosis and prediction of treatment response.

TREATMENTS

Shunting

Shunting procedures for iNPH include ventriculo-peritoneal (VP), lumbo-peritoneal (LP), and ventriculo-atrial (VA) shunts. Of these, VP and LP shunts are the most common, while VA shunts are less common^[35]. There is no significant difference in efficacy and complications between LP and VP shunts, and the technique considered most appropriate for each case is selected^[36]. LP shunts do not puncture the brain and are considered safe in elderly patients, but are not suitable for patients with scoliosis, peritonitis, severe constipation, or obesity^[37].

VP shunts are often chosen when LP shunts cannot be performed for the above reasons. Although VA shunts are used in fewer cases than LP and VP shunts, as described above, it is reported that adverse events and dysfunctions are less common than with VP shunts^[38,39]. Endoscopic transtentorial ventriculostomy (ETV), which differs from the above shunting techniques, should also be described. ETV is a procedure to create a short-circuit pathway to avoid an obstruction in the ventricle. Traditionally, ETV has had narrower indications than shunting. However, recent studies have shown that ETV may improve not only CSF outflow, but also the compliance of the periventricular wall parenchyma^[40-42]. Thus, iNPH surgeries continue to be investigated according to their theoretical bases and actual results to determine the best method. Although the safety of the above-mentioned shunt surgeries has improved over the years, adverse events are still common. A previous study showed that re-operations due to problems such as

infection are more frequently associated with adverse events than first-time shunting procedures^[43].

The two main types of shunt valves currently in use are pressure-fixed and pressure-variable valves. Pressure-fixed valves have a simpler mechanism and are cheaper.

However, variable-pressure valves allow pressure to be set non-invasively from outside the body after shunt placement. The 2020 Cochrane Systematic Review did not show any superiority or inferiority between these two shunt valves^[44]. However, the Japanese Guidelines for Idiopathic Normal Pressure Hydrocephalus, 3rd edition, recommend the use of variable valves for safety reasons^[45]. In addition, antimicrobial-impregnated catheters have recently been used in many cases to prevent shunt infection. Previous studies have shown that antimicrobial-impregnated catheters significantly reduce shunt reconstruction associated with infection^[46]. Therefore, the use of antimicrobial-impregnated catheters may be beneficial in shunt surgery in infection-prone children and immunocompromised patients.

Pharmacotherapy

As discussed in the section on surgery, surgical treatment is associated with ¹side effects and complications. If a tap test does not show clear improvement in cognitive function, surgery is not necessary. If surgery is not performed, the treatment of patients with iNPH is limited to symptomatic treatment. This section describes symptomatic pharmacotherapy.

First, there are anti-dementia drugs. These anti-dementia drugs inhibit the progression of cognitive decline but do not improve cognitive function. Four anti-dementia drugs are used in Japan: donepezil, galantamine, rivastigmine, and memantine. All of these are indicated for Alzheimer's disease, while only donepezil is also indicated for dementia with Lewy bodies. Clinically, these anti-dementia drugs are often prescribed for patients with other types of dementia, including iNPH. However, there is no clear evidence on their efficacy. Therefore, below we introduce the previous case reports. Moriuchi *et al.*^[47] reported that donepezil was effective in four patients with iNPH with

residual cognitive decline after shunting surgery. Takaya^[48] reported a case report in which memantine was effective for psychiatric symptoms of iNPH. Basic experiments also suggest that memantine may reduce hydrocephalus-induced neurodegenerative disorders^[49]. Goreisan is a herbal medicine that regulates water metabolism and has been reported to be effective in normal pressure hydrocephalus^[50]. However, there are no standard guidelines or large-scale studies to support the use of Goreisan for the treatment of iNPH. Furthermore, low-dose acetazolamide, also a diuretic, was reported to restore periventricular leukomalacia in a small case series of patients with iNPH^[51].

1 EPILEPSY

Recently, there has been a focus on patients with older-onset epilepsy, who often present at outpatient dementia clinics^[52]. Previous studies have shown that postoperative complications of iNPH include seizures, although these are rare, occurring in only 0.16% of cases^[53]. Two case reports have been published on nonsurgical iNPH presenting with seizures. In the first case, hyponatraemia associated with the administration of laxatives following lower gastrointestinal endoscopy triggered an epileptic seizure^[54]. In the other case, a change in diagnosis and treatment from donepezil treatment for Alzheimer's disease to levetiracetam treatment for symptomatic epileptic seizures associated with iNPH resulted in improved cognitive function^[55].

CONCLUSION

Promptness and individualisation are needed in the treatment of iNPH. In particular, the fact that suspected iNPH is defined solely by age and imaging findings leads to a more rapid diagnosis. Other novel indicators such as z-EI, BVR, and Rad scale have increased the sensitivity and specificity of the diagnosis. In terms of individualisation, research on biomarkers in spinal fluid has also developed. This has enabled the effect of shunting to be predicted preoperatively.

In addition, further research is needed on drug therapy in cases where surgery is not expected to improve symptoms. The development of biomarkers for less invasive samples such as urine and blood is also expected in the future.

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SIMILARITY INDEX

PRIMARY SOURCES

1

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