Perspective

Clinical tips in diagnosing idiopathic normal pressure hydrocephalus: a new concept beyond the cerebrospinal fluid tap test

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Accurate diagnosis of idiopathic normal pressure hydrocephalus is important to manage patients with idiopathic normal pressure hydrocephalus more appropriately. Based on the clinical features and brain magnetic resonance imaging findings, the idiopathic normal pressure hydrocephalus diagnosis is made up. However, most clinicians do not recommend the shunt operation to their patients with presumed idiopathic normal pressure hydrocephalus unless any patients with idiopathic normal pressure hydrocephalus show a considerable improvement through the cerebrospinal fluid tap test. The cerebrospinal fluid tap test is an invasive method and has some limitations to diagnose idiopathic normal pressure hydrocephalus. Therefore, we suppose that a new diagnostic approach of idiopathic normal pressure hydrocephalus is necessary. Various magnetic resonance imaging findings suggesting idiopathic normal pressure hydrocephalus have been applied to diagnose idiopathic normal pressure hydrocephalus. Besides, advances in neuroimaging techniques, including dopamine transporter imaging, and amyloid imaging may allow clinicians to exclude the potential misdiagnosis including Parkinsonian disorders and Alzheimer's disease in patients with presumed idiopathic normal pressure hydrocephalus. Herein, we suggest a neuroimaging-supportive algorithm for the diagnosis of idiopathic normal pressure hydrocephalus. We suspect that this is the time to change the classical approach of diagnosing idiopathic normal pressure hydrocephalus.

Keywords

Amyloid imaging; Dopamine transporter imaging; Normal-pressure hydrocephalus; Magnetic resonance imaging

1. Introduction

Idiopathic normal pressure hydrocephalus (iNPH) is a potentially treatable disorder. Therefore, early suspicion and accurate diagnosis are important in managing patients with iNPH more appropriately. It is widely accepted that patients with iNPH commonly reveal the classic symptom triad of gait disturbance, cognitive decline, and urinary disturbance. Their neuroimaging findings with computed tomography (CT) or magnetic resonance imaging (MRI) should show an enlarged ventricle (defined as the Evans' index of more than 0.3) [1, 2]. However, the diagnosis of iNPH is difficult in the actual clinical setting. The diagnosis of iNPH could be made by excluding other diagnoses, including neurodegenerative parkinsonian disorders, since patients with iNPH could present with variable degrees of iNPH-mimicking symptoms, including gait disturbance and dementia [3]. Important differential diagnoses of iNPH include vascular parkinsonism (VP), progressive supranuclear palsy (PSP), multiple system atrophy (MSA), dementia with Lewy bodies (DLB), and Alzheimer's disease (AD) [3, 4].

2. Necessity of a new concept for the diagnosis of iNPH

The cerebrospinal fluid (CSF) tap test is widely accepted as a good predictive marker for surgical outcomes of iNPH [1, 5]. Accordingly, many clinicians bind the idea that this invasive method is the confirmational step for the diagnosis of iNPH before shunt surgery. Once one patient is regarded as having clinically possible iNPH, subsequently, the patient allows undergoing lumbar puncture for transient or continuous CSF drainage to evaluate an improvement of clinical symptoms, including gait disturbance. However, the problem is that an excellent response to the CSF tap test in certain patients with iNPH does not guarantee the surgical outcome in actual clinical settings since the CSF tap test has a variable degree of sensitivity (42~93%) and specificity (20~100%) [6–11]. One reason for the mismatch between an excellent response to the CSF tap test and no clinical improvement with shunt surgery in the same individual with suspected iNPH is probably due to a false-positive result of the CSF tap test, since the test lacks a sham trial. In other words, the CSF tap test might inevitably have a placebo effect, resulting in some degree of unreliability. Occasionally, clinicians including us might have experiences of feeling embarrassed or disappointed when the surgical treatment such as the ventriculoperitoneal shunt operation did not lessen the clinical symptoms of some patients with clinically suspected iNPH. However, those patients showed an excellent response to the CSF removal test.

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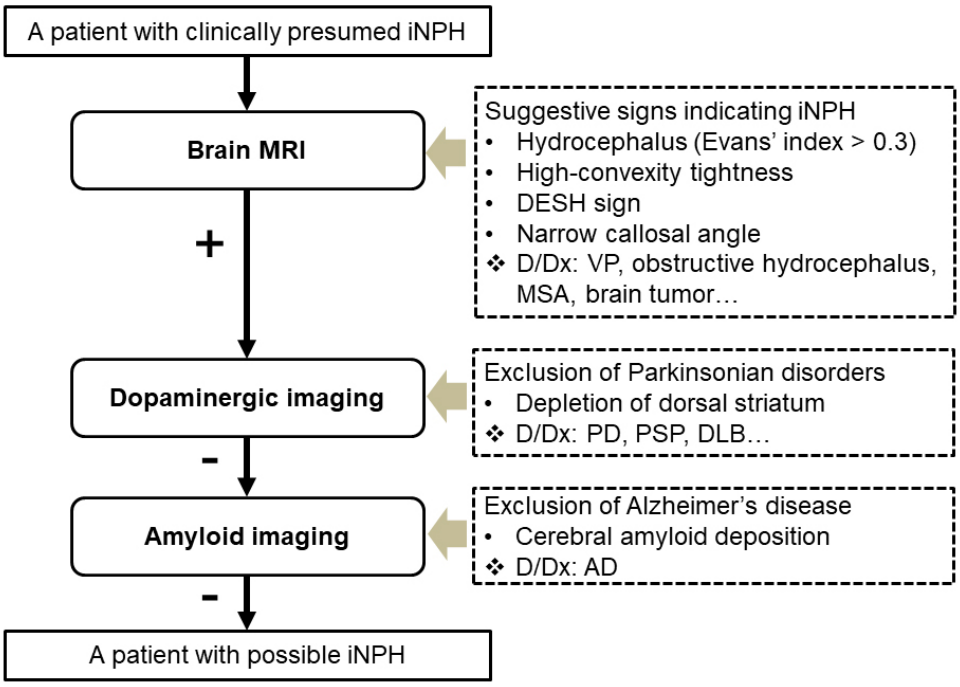

Fig. 1. Diagnostic approach of patients with presumed idiopathic normal pressure hydrocephalus (iNPH).

Clinicians suffer more failure in the treatment of iNPH, and clinicians tend to be more reluctant to diagnose iNPH. On the contrary, it might be possible that clinicians may give up the surgical treatment to any patient with iNPH, unless clinicians are fully satisfied with the result of the CSF tap test. Then, the patient with iNPH might not have any opportunity to lessen his or her symptoms induced by iNPH. However, we suppose that clinicians should be aware of the insufficient sensitivity of the CSF tap test. Thereby we do not need to get frustrated with the result of the CSF tap test. In addition, some centers have performed other ancillary invasive tests, combined with the CSF tap test, including the prolonged lumbar and/or infusion tests (either lumbar or ventricular) in patients with presumed iNPH. However, the CSF tap test and those evaluations for CSF hydrodynamics resulted in considerable limitations for the diagnosis of iNPH yet. Such tests are invasive, and the positive predictive value ranges from 62~90% [12–14]. Therefore, a noninvasive and alternative approach is necessary to increase the diagnostic accuracy of iNPH, especially when the result of the CSF tap test and/or other ancillary tests including the CSF infusion test, is ambiguous to conclude in patients with presumed iNPH.

We have expanded our understandings of the diagnosis and treatment of iNPH through our own experiences [15–20]. Herein, we aim to introduce a new concept for the diagnosis of iNPH, not only based on the clinical symptoms of iNPH but also MRI-supported features. In addition, in the clinical evaluation of iNPH, we include *in vivo* molecular imaging modalities, including dopamine transporter (DAT) imaging and beta-amyloid imaging. The majority of patients with iNPH have performed the CSF tap test with CSF dynamics imaging using serial metrizamide CT cisternography in our movement disorder clinic to have more confidence in the clinical diagnosis of iNPH. However, we have experienced that the CSF tap test did not give us noticeable results for performing the shunt surgery in a considerable number of patients with presumed iNPH. Instead, our neuroimaging-based approach has made us decide to perform shunt surgery in those patients. In line with the literature [21], we are no longer dependent on the responsiveness of the CSF tap test before the shunt operation.

3. Clinical tips for neuroimaging biomarkers: MRI and molecular imaging

The characteristic MRI findings including disproportionately enlarged subarachnoid space hydrocephalus (DESH), have been applied to diagnose iNPH as a newly accepted neuroimaging biomarker of iNPH [2, 5]. Significantly, the DESH sign on the coronal view has related to a good outcome of surgical treatment in patients with iNPH [4]. In addition, callosal angle narrowing on the coronal view could give clinicians more confidence in the diagnosis of iNPH in combination with the DESH sign. On the other hand, the only finding of the DESH sign occasionally seems insufficient to diagnose iNPH in certain patients with iNPH [22, 23]. In such cases with iNPH, an additional finding of Evans' index >0.3 might be helpful to increase the diagnostic accuracy of iNPH [23]. Besides, in line with the literature [24], we have observed that close high-convexity sign might be the earliest finding on axial images of MRI in patients with iNPH. Therefore, high-convexity tightness is suggested as an early and reliable MRI biomarker of iNPH [21]. Taken together, we could di-

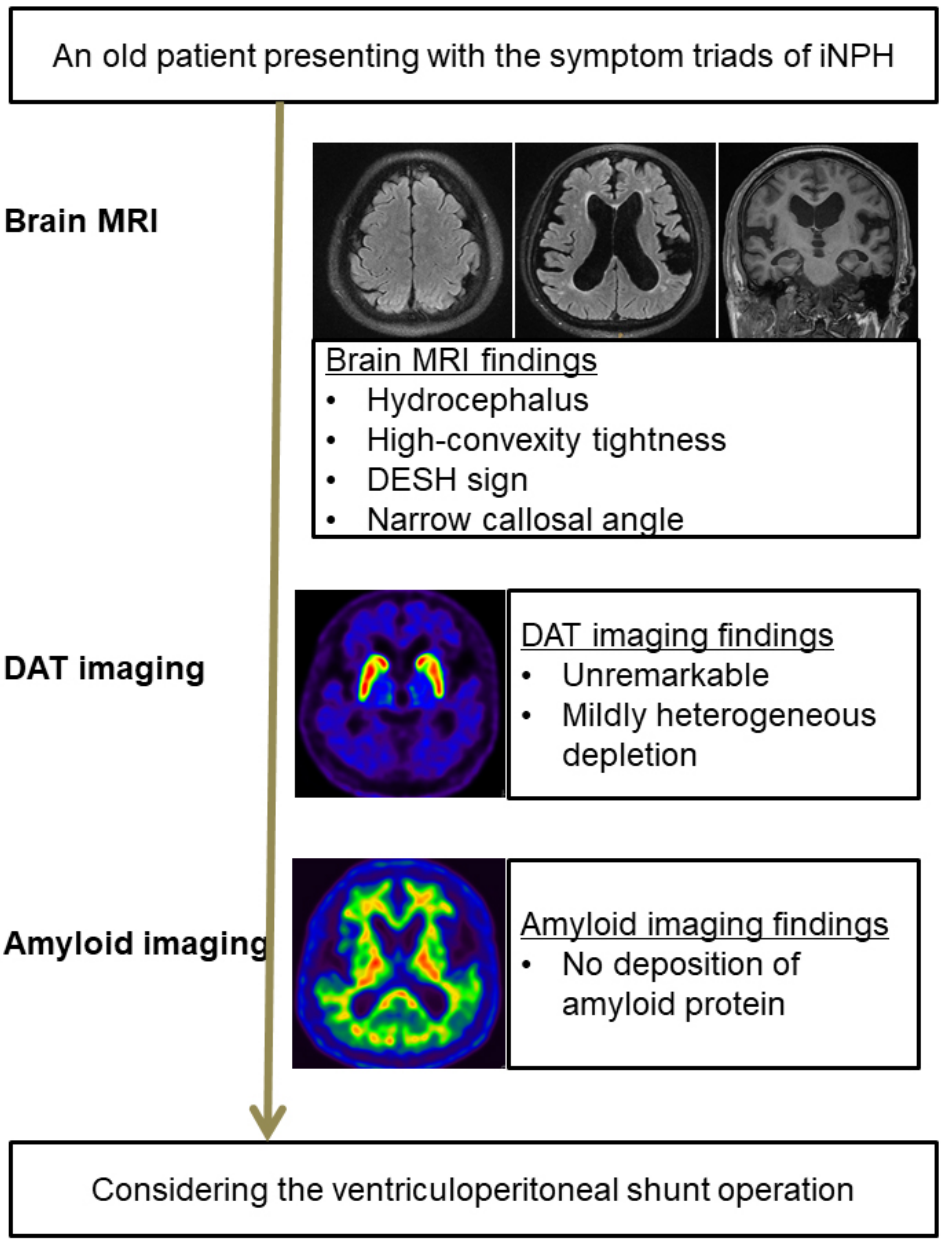

Fig. 2. Diagnostic schema with an illustrative case with iNPH.

agnose iNPH based on the indicative MRI biomarkers including Evans' index, tight high-convexity, DESH sign, and callosal angle narrowing.

Recently, *in vivo* molecular imaging techniques may enable the detection of pathological information of patients in natural clinical settings. Besides, compared with single-photon emission computed tomography (SPECT) imaging, positron emission tomography (PET) imaging has an advantage in localization in the brain. It has been widely accepted that dopamine transporter (DAT) imaging using PET is a highly sensitive modality in diagnosing neurodegenerative parkinsonian disorders, including PD, PSP, MSA, and DLB [25, 26]. Therefore, it is highly recommended that patients with iNPH perform DAT imaging to exclude neurodegenerative parkinsonian disorders before shunt surgery. DAT findings in patients with iNPH may show mildly heterogeneous depletion of the striatum, especially in the caudate nucleus [15], distinguishing from the findings of Parkinsonian disorders [26]. In addition, amyloid PET imaging could contribute to excluding the possibility of AD in patients with iNPH. In actual clinical settings, older people having AD comorbid with musculoskeletal problems might be presented as iNPH mimics. Therefore, it is necessary to undergo amyloid imaging in patients with presumed iNPH to exclude the possibility of AD. However, patients with early stages of AD usually do not exhibit significant gait disability, an initial symptom of iNPH.

Collectively, we propose that neuroimaging-based approaches through brain MRI, DAT, and amyloid imaging should be regarded as a non-invasive alternative model to diagnose iNPH (Fig. 1). If clinicians evaluate patients with iNPH according to our diagnostic algorithm, we suppose clinicians diagnose iNPH more efficiently (Fig. 2).

However, a review study showed the limited role of PET imaging for the diagnosis of iNPH, and clinicians should not overestimate the usefulness of dopaminergic PET imaging or amyloid PET imaging [27]. Dopaminergic PET studies showed that striatal dopaminergic reduction was associated with the severity of gait disturbance [28]. Its restoration was related to the amelioration of gait disturbance in patients with iNPH [29]. Besides, amyloid pathology could be seen up to about 57% in patients with iNPH and certain patients with amyloid pathology may reveal a shunt response. However, it has been accepted that amyloid-positive patients with iNPH did not have good clinical outcomes after VP shunt surgery, compared with amyloid-negative patients with iNPH [27]. Therefore, patient selection for performing shunt surgery in patients with iNPH needs to be cautious.

4. Clinical features and shunt surgery in patients with advanced NPH

The natural course of patients with iNPH remains little known. Indeed, the clinical diagnosis of iNPH in many past studies might not be accurate unless the studies applied the recent criteria of iNPH using the MRI-supported features [2, 5]. Toma and colleagues [30] reported that most patients with iNPH experienced neurological deteriorations without shunt surgery. Likewise, we occasionally encounter patients with a long history of iNPH who have not performed shunt surgery, resulting in 'hydrocephalic astasia-abasia' with mutism or abulia state. Some with iNPH were not previously indicated for the shunt operation by other clinicians because they did not significantly improve clinical symptoms in the CSF tap test. Others with iNPH would not take the shunt operation in regards to intraoperative and perioperative risks.

Meanwhile, in such cases who gave up surgery, one of the main reasons was associated with the low confidence of clinicians on the success of the shunt surgery. Suppose clinicians could rule out other possibilities, including Parkinsonians disorders or AD, by performing both DAT and amyloid imaging before the shunt surgery. In that case, the shunt operation might be performed in more patients with iNPH.

Up to date, in our movement disorder clinic, several cases with late stages of iNPH (i.e., a bedridden state with no verbal output) underwent shunt surgery. All of them revealed the characteristic findings of iNPH on brain MRIs. Moreover, they exhibit neither the depletion of the dorsal striatum on DAT imaging nor beta-amyloid deposition in the cerebral cortex on amyloid PET imaging. We performed shunt surgery to such hopeless patients with iNPH, not only because we were convinced of the diagnosis of iNPH but also because their families wanted to have an opportunity to alter the vegetative state-like status of patients with advanced iNPH. After the surgical treatment, most of them could speak phrases or sentences, although their astasia-abasia was not considerably improved (our observations).

5. Conclusions

The traditional concept of the diagnosis of iNPH is needed to be updated and is changing now in line with the technological evolution of neuroscience, including molecular neuroimaging. Based on the characteristic MRI findings of iNPH, clinicians could distinguish iNPH from iNPH-mimics. Furthermore, clinicians could exclude the possible comorbidity of neurodegenerative parkinsonian disorders and AD in patients with presumed iNPH before shunt surgery using DAT imaging and amyloid imaging. We hope, through this paper, many clinicians could manage their patients with iNPH more properly appropriately.

Abbreviations

AD, Alzheimer's disease; CSF, cerebrospinal fluid; CT, computed tomography; DAT, dopamine transporter imaging; DESH, disproportionately enlarged subarachnoid space hydrocephalus; DLB, dementia with Lewy bodies; iNPH, idiopathic normal pressure hydrocephalus; MRI, magnetic resonance imaging; MSA, multiple system atrophy; PD, Parkinson's disease; PET, positron emission tomography; PSP, progressive supranuclear palsy; SPECT, single-photon emission computed tomography; VP, vascular parkinsonism.

Author contributions

Conceptualization, KYK. Methodology, SML and KYK. Data curation, SML and KYK. Formal analysis, SML and KYK. Funding acquisition, SML and KYK. Investigation, SML and KYK. Writing—original draft, SML and KYK. Writing—review & editing, SML and KYK. Supervision, KYK. All authors have read and agreed to the published version of the manuscript.

Ethics approval and consent to participate

All procedures were performed according to ethical standards of the institution and/or the national research committee and the 1964 Helsinki Declaration and its subsequent amendments. Written informed consent is not needed in this type of article.

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Conflict of interest

The authors have no conflicts of interest relevant to this study to disclose.

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