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Challenges in diagnosing normal pressure hydrocephalus: Evaluation of the diagnostic guidelines

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ABSTRACT

Purpose: To evaluate the present diagnostic guidelines of idiopathic normal pressure hydrocephalus (iNPH) in a sample from the general population.

Methods: A total of 168 individuals (93 females, 75 males), mean age 75 years (range 66–92) with and without symptoms of iNPH underwent a CT-scan of the brain, a neurological examination with assessment of the triad symptoms, i.e. gait disturbances, memory impairment and urgency incontinence. The participants were then diagnosed as "unlikely", "possible" and "probable" iNPH according to the American-European and the Japanese guidelines, respectively. Separately, a senior consultant in neurology diagnosed each patient based on the overall clinical picture.

Results: Obtaining a diagnosis of "probable iNPH" was three times more likely according to the American-European guidelines (n = 35) compared to the Japanese guidelines (n = 11) or the neurologist (n = 11). The concordance was highest (Kappa = 0.69) between the Japanese guidelines and the neurologist.

Conclusions: Considerable discrepancies were found when diagnosing iNPH according to two international guidelines and a neurologist, respectively. The Japanese guidelines, which include a minimum of two triad symptoms, were most concordant with the neurologist. As a step towards widely accepted, standardized diagnostic criteria, we suggest a revision of the current guidelines, preferably into one common diagnostic system.

1. Background

Idiopathic normal pressure hydrocephalus (iNPH) is a syndrome with gait disturbance, cognitive impairment and urinary symptoms that may resemble other disorders among elderly such as Parkinson's and Alzheimer's disease but have a characteristic neuroradiological picture [1,2]. The reported prevalence of iNPH varies from 0.5% to 2.9% in the elderly population [3] It is essential to identify patients with iNPH as 70–80% improve by ventricular shunting [4]. A recent study shows improvements in quality-adjusted life years and general cost effectiveness [5].

INPH still lacks widely accepted, standardized diagnostic criteria. Two independent committees of experts have come up with separate diagnostic guidelines with the aim to attain a more accurate and coherent way of diagnosing the disease [1,6].

A recent review article highlighted the design heterogeneity and use of separate diagnostic criteria among published epidemiological studies on iNPH [3]. Furthermore different scales have been used for measuring the severity of symptoms, ranging from visual inspection of gait patterns to more objective measurements of gait speed and number of steps [7,8]. Current guidelines are based upon assessments of clinical symptoms, however which tests that should be used as well as the cut-off limits between normal and impaired function have not yet been specified. Investigations of Cerebrospinal fluid dynamics are often performed as supplemental tests in diagnosing iNPH, however the value has been questioned [9,10].

The lack of a golden standard for the diagnosis of iNPH is problematic both in clinical practice and epidemiological research, therefore this study aimed to evaluate the diagnostic guidelines for iNPH in a sample from the general population. Specific aims were to find out the concordance between iNPH diagnoses according to the two diagnostic guidelines [1,6] and a neurologist, and explore the relation between the diagnoses and the degree of disability.

2. Material and method

2.1. Study population

This study is part of an ongoing population-based prospective study

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Table 1
Diagnostic criteria according to two separate international guidelines.

A. American-European guidelines [1]

	Probable[a]	Possible	Unlikely
Clinical features:	Gait/balance disturbance and at least one of the following: a) Cognitive impairment b) Urinary incontinence/urgency	Symptoms of either: a) Incontinence and/or cognitive impairment in the absence of gait/balance disturbance b) Gait disturbance alone	No component in the clinical triad or symptoms explained by other causes
Brain imaging	Ventriculomegaly (EI > 0.3) and at least one of the following: a) Narrow callosal angle b) Enlargement of the temporal horns c) Periventricular signal changes not attributable to ischemic changes or demyelination	Ventriculomegaly (EI > 0.3)	No evidence of ventriculomegaly

B. Japanese guidelines [6]

	Possible with MRI support	Possible	Unlikely
Clinical features	At least two of the clinical triad: Gait disturbance, cognitive impairment and urinary incontinence	At least two of the clinical triad: Gait disturbance, cognitive impairment and urinary incontinence	None of this
Brain imaging	Ventriculomegaly (EI > 0.3) and the following: a) Narrowing of the sulci over the high convexity/DESH [21]	Ventriculomegaly (EI > 0.3)	No evidence of ventriculomegaly

EI = Evans Index, DESH = Disproportionately enlarged subarachnoid space hydrocephalus.
[a] Not including the criteria ICP ≤ 20.

aimed to establish the prevalence of iNPH among the elderly. Using the Swedish population register to obtain participants, 1000 randomized individuals over the age of 65 living in the region of Jämtland Härjedalen (total of 28.000) were asked to participate in the study and answer a simple symptom questionnaire. A total of 673 individuals completed the questionnaire. Based on the questionnaire replies, a subgroup was selected for further examination at the neurological department at Östersund's Hospital between August 2014 and October 2015. The inclusion criteria for further clinical evaluation were a mandatory gait or balance impairment in addition to at least one more symptom. A total of 166 individuals met the inclusion criteria, 117 of these completed the study. Of the remaining 49, 27 withdrew or had incomplete testing, 20 were excluded because of severe neurological disorders such as hemiparesis after stroke, severe MS, brain tumor or Parkinson disease, diagnosed by neurologist and without ventriculomegaly. Two deceased before further investigations. A randomly selected group consisting of 51 people who reported less than two symptoms on the questionnaire, including 5 with an invalid combination of two symptoms, underwent the same tests giving a final study population of 168 individuals.

The ethical committee at Umeå University approved the study in 2014 (Dnr 2014/180-31).

2.2. Clinical and radiological examination

All study participants underwent computed tomography (CT) of the brain, neuropsychological and neurological examination. The neuropsychological assessment included Ray auditory verbal learning test (RAVLT), Grooved pegboard test, Swedish Stroop test and the Mini Mental state examination (MMSE) [11–14]. The clinical examination comprised Romberg's test, 10-metre walking test and evaluation of balance and gate with ordinal scales [12,15,16]. Urinary symptoms were rated by self-report with the Continence Scale [12]. The radiological features assessed were Evans index, callosal angle, size of temporal horns, periventricular hypodensites and DESH (Disproportionately enlarged subarachnoid space hydrocephalus) [17–21] Cerebrospinal fluid measurements were not performed.

The radiological and clinical evaluations were blinded i.e. those performing the clinical evaluations did not have access to the results of the CT scans and vice versa. The results from the clinical tests were graded according to a syndrome specific iNPH scale which consists of four independent domains; gait, balance, continence and neuropsychology with scores ranging from 0 to 100. A lower score corresponds to more symptoms [12].

A senior consultant in neurology (KL) with many years of experience of iNPH made a clinical diagnosis based on an overall assessment of radiology and symptoms, independent of any guidelines. In contrast, to avoid subjective use of the international guidelines (Table 1), fulfilments of each criterion were based strictly on the results of the clinical measurements with predefined cut-off limits between normal and impaired function. The cut-off levels for the radiological markers callosal angle (< 90°) and Evans index (> 0.30) were based on the literature [17,22] Cut-off levels for clinical symptoms were determined by optimizing sensitivity and specificity with the neurologist's diagnosis serving as the gold standard. For example, a MMSE value of < 28 was defined as pathological (Fig. 1). The corresponding cut-off level for the median size of the temporal horns was ≥ 4 mm and the cut-off scores

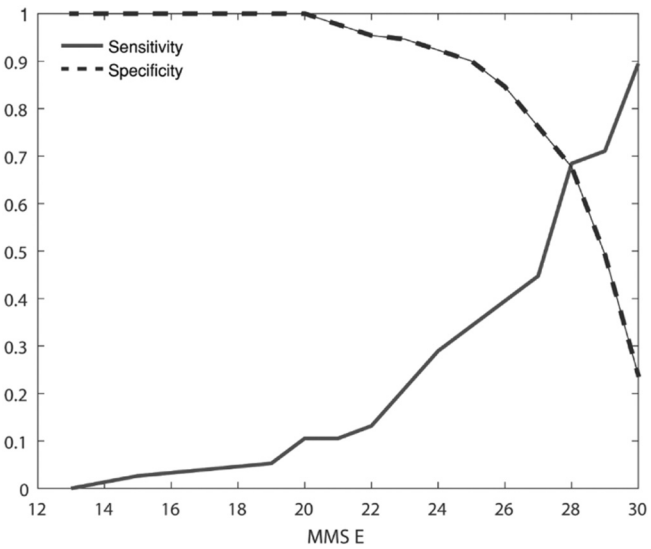

Fig. 1. Sensitivity and specificity for different MMSE values.

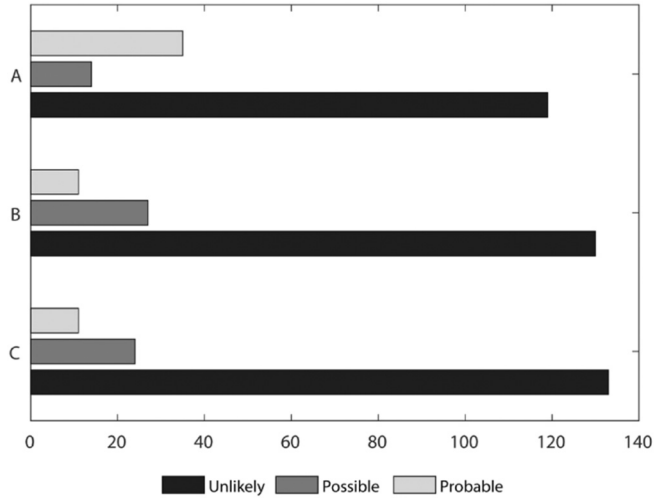

Fig. 2. Number of individuals diagnosed as "probable", ¨possible¨ and ¨unlikely¨ iNPH according to American-European guidelines (A), Japanese guidelines (B) and Neurologist's diagnosis (C).

for the iNPH scale were; gait domain < 86, balance domain < 83, continence domain < 100 and neuropsychology domain < 80, respectively.

Finally, we used the modified Rankin scale (mRS) [23] to evaluate the degree of disability. The scale ranges from 0 to 6; where 0 = "no symptoms"; 1 = "no significant disability, able to carry out all usual activities"; 2 = "slight disability, able to look after own affairs without assistance"; 3 = "moderate disability, requires some help"; 4 = "moderately severe disability, unable to attend to own bodily needs"; 5 = "severe disability, requires constant nursing care, bedridden"; 6 = "dead".

2.3. Statistical methods

Data are presented as number of individuals with iNPH according to the two diagnostic guidelines and the neurologist's diagnosis. Cohen's Kappa was used for the concordance between these three different diagnostic systems. The Kruskal-Wallis test was used for analyzing differences between the diagnostic groups. The cut-off levels for clinical symptoms were determined by optimizing sensitivity and specificity. Analysis were performed using SPSS (version 23) and graphs were made using Matlab (version R2016). The level of significance was set to < 0.05.

3. Results

The sample consisted of 168 individuals, (93 females, 75 males), mean age 75 years (range 66–92 years). Out of them, 119, 130 and 133 were diagnosed as "unlikely" iNPH according to the American-European guidelines (AEG), the Japanese guidelines (JG) and the neurologist, respectively. A higher number of patients were diagnosed as "probable" iNPH according to AEG ($n = 35$) than according to JG ($n = 11$) and the neurologist ($n = 11$) ($p < 0.001$) (Fig. 2).

The concordance was highest between the Neurologist's diagnosis and JG. (Kappa = 0.69) and lowest between the Neurologist's diagnosis and AEG. (Kappa = 0.44) (Table 2). Notable is that nine cases were classified as "probable" iNPH according to AEG but as "unlikely" iNPH by the neurologist. A further analysis of these nine cases revealed that they obtained the diagnosis of "probable" iNPH because of ventriculomegaly (Evans Index > 0.3) in combination with wide temporal horns (> 4 mm) or periventricular hypodensities. According to JG they were classified as "possible" iNPH due to the absence of the radiological criterion of DESH (Disproportionately enlarged subarachnoid space hydrocephalus) [21] (Table 2). In contrast, the neurologist found these cases as "unlikely iNPH" due to reasons as; signs of Alzheimer's disease, mild and age appropriate symptoms. In two cases, a previous ischemic lesion and a congenital anatomical anomaly explained the higher Evans index.

The level of disability (mRS) was significantly higher for those with

Table 2
Concordance between the two international guidelines (A) and between a neurologist's diagnosis and international guidelines (B), (C).

A. American-European guidelines [1]

Japanese guidelines [6]		Unlikely	Possible	Probable	Total
	Unlikely	119	11	0	130
	Possible	0	3	24	27
	Probable[a]	0	0	11	11
Total		119	14	35	168
Kappa Value	0.51, fair [24]				

B. Neurologist's diagnosis

Japanese guidelines [6]		Unlikely	Possible	Probable	Total
	Unlikely	123	7	0	130
	Possible	10	16	1	27
	Probable[a]	0	1	10	11
Total		133	24	11	168
Kappa Value	0.69, good [24]				

C. Neurologist's diagnosis

American-European guidelines [1]		Unlikely	Possible	Probable	Total
	Unlikely	114	5	0	119
	Possible	10	4	0	14
	Probable	9	15	11	35
Total		133	24	11	168
Kappa Value	0.44, fair [24]				

[a] Probable = "possible with MRI support" criteria according to Japanese guidelines [6].

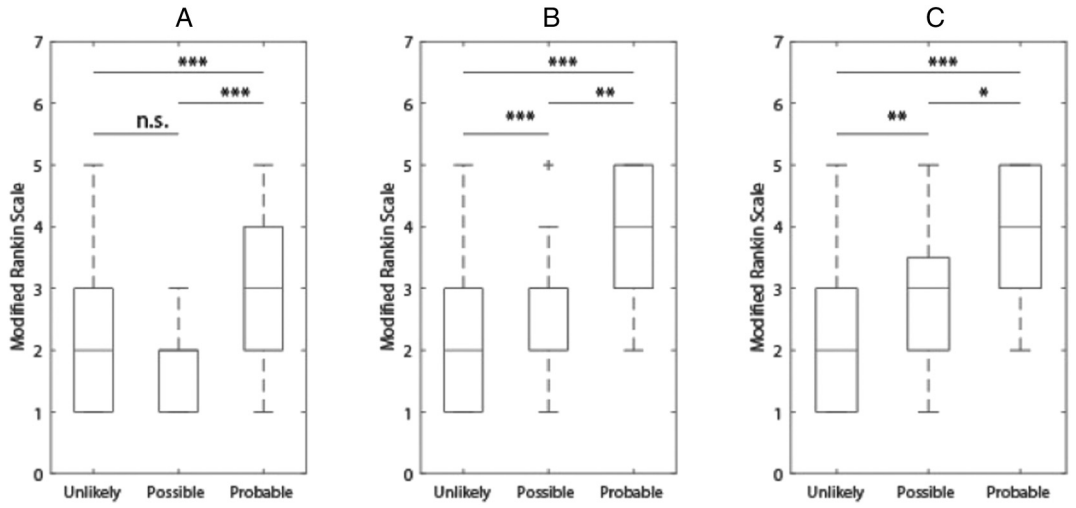

Fig. 3. The level of disability (mRS) for those with "unlikely", "possible" and "probable" iNPH according to American-European guidelines (A), Japanese guidelines (B) and Neurologist's diagnosis (C).

"possible" than those with "unlikely" iNPH according to JG or the Neurologist's diagnosis ($p < 0.05$) whereas this was not the case with AEG (Fig. 3).

4. Discussion

In this sample of 168 individuals, obtaining a diagnosis of "probable" iNPH, was more than three times more likely with the American European guidelines (AEG) [1] than the Japanese guidelines (JG) [6]. Most restrictive in diagnosing iNPH was the senior consultant in neurology. The concordance of the diagnoses was highest between JG and the neurologist. The level of disability was higher in those with iNPH than in those without, except for "possible" and "unlikely" iNPH according to AEG which did not show any significant difference in disability.

Nine individuals obtained the diagnosis of "probable" iNPH according to AEG and at the same time "unlikely" iNPH according to the neurologist. In these cases, an atypical radiological and clinical picture explained the differences.

Diagnoses according to AEG were less concordant with the other two diagnostic methods. One possible explanation for this is that the clinical and radiological criteria for obtaining a iNPH diagnosis according to AEG are not specific enough, with risk of including individuals with other conditions than iNPH. The mandatory radiological criteria for obtaining a "possible" diagnosis for both guidelines is ventriculomegaly, i.e. Evans index > 0.3. However, according to AEG one symptom of the clinical triad is sufficient, whereas JG requires at least two. This could be one explanation to why the groups of "unlikely" and "possible" iNPH according to AEG showed no significant difference in the degree of disability.

Fulfilment of the criteria for "probable" iNPH according to AEG, requires at least two triad symptoms and ventriculomegaly in combination with either of; wide temporal horns, periventricular signs of altered water content, or a narrow callosal angle. However, it is stated that these radiological changes should not be entirely attributable to atrophy and, in the case of periventricular hypodensities, to ischemia. The drawback is that such judgments are more or less subjective and depend on the radiologist's experience. In addition, mild atrophy and small vessel disease are common in this age group, and the latter have been shown to be overrepresented in patients with iNPH [25,26]. A narrow callosal angle, seem to be a more iNPH specific radiological feature than the others [27,28]. Unfortunately, the cut-off value that is stated in the guidelines (> 40°) has no support in previous literature and might be a printing mistake [18,22,28].

The diagnosis of "possible iNPH with MRI support" (JG) requires two triad symptoms, ventriculomegaly and the additional radiological sign of DESH. DESH is considered an iNPH specific pattern that does not occur in brain atrophy [21,29]. An advantage with this diagnosis is that measurements of CSF opening pressure are not required, which enables larger population based studies on iNPH.

To be able to compare the results between epidemiological and other research studies of iNPH, one internationally acknowledged diagnostic system would be valuable. According to a systematic review, only 6 out of 15 published studies adhered to existing diagnostic guidelines [3]. Out of these, 2 adhered to AEG, and 4 to JG. Our finding of a modest concordance between these two guidelines, underlines the need for caution when comparing prevalence numbers between studies.

Another challenge for diagnosing iNPH in a uniform and standardized way is the evaluation of clinical symptoms. Different assessment scales have been developed [12,30–34] but unfortunately there is no consensus of which scale to use. Neither are there any statements on the degree of symptoms needed to fulfil the diagnostic criteria of for example gait disturbance or cognitive impairment. In this study, we tried to overcome such obstacles with the use of Hellström's iNPH symptom scale [12] and ROC curves to obtain acceptable cut-off values. However, these values are calculated for the present study population and might not be generalizable to other populations.

This study included elderly from the general population with common comorbidities such as osteoarthrosis, spinal stenosis and dementia. Although this increases generalizability, it might be a limitation, and explain the occurrence of gait impairment, cognitive decline and disability also in the subjects with an "unlikely" iNPH diagnosis. To avoid inclusion-bias, the mRS scale was used as an independent marker of the disease grade. This assumes that more iNPH symptoms leads to a higher level of disability, which is probably correct. One drawback with the mRS scale is that the step between the different levels of disability is large, making it less sensitive to changes.

Another limitation is that measurements on CSF opening pressure were not performed as we considered it to be too invasive for a population based study. According to both guidelines, the CSF opening pressure should be 20 cm H_2O or less to fulfil the criteria for "probable" iNPH. However, this criterion might be questioned, as the evidence for this exact cut-off is weak and opening pressures slightly above 20 cm H_2O exist in iNPH. To rule out obstructive hydrocephalus, neuroradiology should be used instead.

In summary, considering that many elderlies suffer from multiple conditions with overlapping symptoms, the criteria for obtaining a iNPH diagnosis should be as objective and specific as possible.

Diagnostic improvements could probably also be achieved with grading of the iNPH associated radiological changes [17,18,28,29] and standardized symptoms scales, with population based reference values for normal and impaired function.

4.1. Conclusions

Considerable discrepancies were found when diagnosing iNPH according to the two diagnostic guidelines and a neurologist, respectively. The Japanese guidelines, which include a minimum of two triad symptoms, were most concordant with the clinical assessment by a neurologist. We suggest a revision of the present guidelines, preferably into one common diagnostic system.

Declaration of interest

The authors report no disclosures.

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