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SHORT COMMUNICATION

Brain linear measurements for differentiating normal pressure hydrocephalus from Alzheimer's disease: an exploratory study

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Abstract

Background and purpose: Easy and reliable tools for the differential diagnosis between idiopathic normal pressure hydrocephalus (iNPH) and Alzheimer's disease (AD) are needed.

Materials and methods: In this cross-sectional study iNPH and AD patients referred to the Neurology Unit of the University of Catania from 1 January 2020 to 1 December 2022 were enrolled. The following brain linear measurements (BLMs) were calculated: Evan's index (EI), the parieto-occipital ratio (POR) and the temporal ratio (TR). For each index, sensitivity, specificity and the area under the curve (AUC) were calculated. Moreover, a cumulative index, the BLM index, was also considered.

Results: Fifty patients (25 iNPH and 25 AD) were enrolled. In differentiating iNPH from AD, EI had the highest AUC (0.956), POR had the highest specificity (100%) whilst TR had the highest sensitivity (92%). The BLM index differentiated iNPH and AD with a sensitivity of 96%, a specificity of 92% and an AUC of 0.963 with an optimal cut-off value of 0.303.

Conclusion: Evan's index, POR and TR may be useful in the differential diagnosis between iNPH and AD. At an individual level, the BLM index represents a valid and reliable tool to achieve an accurate differentiation between these two conditions.

KEYWORDS
Alzheimer's disease, diagnosis, idiopathic normal pressure hydrocephalus, magnetic resonance imaging

INTRODUCTION

The differential diagnosis between idiopathic normal pressure hydrocephalus (iNPH) and Alzheimer's disease (AD) could represent a challenge [1]. On this basis, indices of ventricular enlargement such as the Evan's index (EI), the parieto-occipital ratio (POR) and the temporal ratio (TR) could be useful. However, whilst several studies have assessed the usefulness of EI [2], only few studies have evaluated the potential role of the TR and the POR in iNPH diagnosis [3].

The aims of the present study were to calculate the accuracy of EI, POR and TR in differentiating iNPH from AD and to develop a new index useful in the differential diagnosis at an individual level.

Antonina Luca and Giulia Donzuso contributed equally.

METHODS

This cross-sectional retrospective study was performed according to the Reporting of Studies Conducted using Observational Routinely Collected Health Data (RECORD) statement.

Patients affected by probable iNPH [4] referred to the Neurology Unit of the University Hospital "Policlinico-San Marco" of Catania from 1 January 2020 to 1 December 2022 were consecutively enrolled and compared to patients affected by probable AD [5] matched by age and disease duration. The study was approved by the local ethics committee (protocol number 72/2021/PO).

Neuropsychological assessment

The following tests were performed: global cognition (Mini-Mental State Examination), episodic memory (Rey's Auditory Verbal Learning Test), executive functioning (Frontal Assessment Battery, Verbal Fluency Test), attention (Stroop color–word test), visuo-spatial functioning (clock drawing test, copy of figures).

Magnetic resonance imaging (MRI) protocol and indices calculation

Brain MRI was performed with a 1.5 T unit (Signa HDxt, GE Medical Systems). A 3D T1-weighted high-resolution spoiled gradient echo sequence with a 1.2-mm slice thickness and an isotropic in-plane resolution of 0.98 mm was acquired. Additionally, all patients underwent T2-weighted and fluid attenuated inversion recovery images to exclude morphological abnormalities.

Magnetic resonance imaging linear measurement

The EI was calculated in the axial scans by dividing the width of the frontal horns (FH) by the maximum width of the inner table of the cranium (bi-parietal inner table, $BIP\text{-}_{EI}$), using Monro's foramens as anatomical neuroimaging landmark and moving on the slices where the FH were the largest (Figure 1a). EI values >0.30 were considered pathological [6, 7].

The POR was calculated as the ratio between the width of the occipital horns (OH) at the atrium and the maximum width of the inner table of the cranium at the same level (bi-parietal inner table, $BIP\text{-}_{POR}$). POR values >0.550 were considered pathological [7] (Figure 1b).

The TR was calculated as the ratio between the width of the temporal horns (TH) at the level of maximal convexity of the hippocampus and the maximum width of the inner table of the cranium at the same level (bi-temporal inner table, BIT) (Figure 1c). TR values >0.07 were considered pathological [7].

A new imaging index, termed brain linear measurement (BLM) index, was developed and calculated in all the enrolled subjects as the ratio of the sum of the linear ventricular measurements and the sum of the bi-parietal and bi-temporal diameters $(FH+OH+TH)/(BIP\text{-}_{EI}+BIP\text{-}_{POR}+BIT)$.

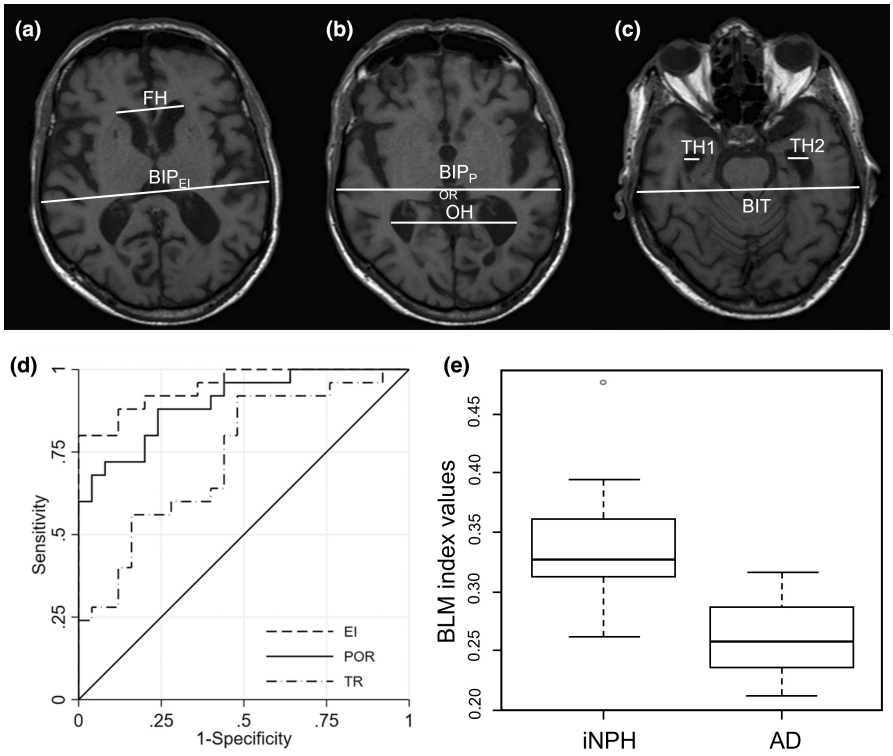

FIGURE 1 MRI linear measurements and analysis. Computation of (a) Evan's index (EI), (b) the parieto-occipital ratio (POR) and (c) the temporal ratio (TR). (d) ROC analysis showing EI AUC 0.956, POR AUC 0.900, TR AUC 0.742. (e) Box plot of BLM index values for iNPH and AD. Outliers are represented by dots. AD, Alzheimer's disease; AUC, area under the curve; BIP_{EI}, bi-parietal inner table of EI; BIP_{POR}, bi-parietal inner table of POR; BIT, bi-temporal inner table; BLM, brain linear measurement; FH, frontal horns; iNPH, idiopathic normal pressure hydrocephalus; MRI, magnetic resonance imaging; OH, occipital horns; TH, temporal horns.

Statistical analysis

Data were analyzed using STATA 16.0 software packages (Stata Statistical Software: Release 16, StataCorp LLC) and Epitools Epidemiological Calculators (http://epitools.ausvet.com.au). Quantitative variables were expressed as mean and standard deviation. Qualitative variables were expressed as number and percentage. The Shapiro–Wilk normality test was performed. Differences between means were evaluated with the unpaired *t* test in the case of normal distribution and the Mann–Whitney *U* test for not-normal distribution. The differences between proportions were evaluated by the chi-squared test. Significance was set at p value <0.05 and 95% confidence intervals were calculated. For each index, a receiver operating characteristic (ROC) curve was developed, obtaining the area under the curve (AUC) and values of sensitivity, specificity and accuracy.

Optimal cut-off level, defined as the value with the highest sum of sensitivity and specificity on the ROC, was calculated using Youden's method for the BLM index.

RESULTS

Twenty-five patients with iNPH and 25 patients with AD were enrolled. No statistically significant differences in terms of age, gender and disease duration were recorded comparing the two groups (Table 1). At the neuropsychological assessment, patients with AD presented significantly lower episodic memory performances than patients with iNPH. No other significant differences were found comparing the two groups in the other cognitive domains.

On MRI, all the three ventricular enlargement measures (EI, POR and TR) were significantly higher in iNPH than AD. Concerning EI, 20 (80%) iNPH patients and 3 (12%) AD patients had a pathological EI value (p value <0.001). EI sensitivity was 80%, specificity 88% and accuracy 84%.

Regarding POR, 6 (24%) iNPH patients and no patients with AD had a pathological POR value; POR sensitivity was 24%, specificity 100% and accuracy 62%.

Concerning TR, 23 (92%) iNPH and 14 (56%) AD patients had pathological TR (p value 0.004). TR sensitivity was 92%, specificity 44% and accuracy 68%.

The AUC values were EI 0.956, POR 0.9 and TR 0.742 (Figure 1d).

The cumulative BLM index was significantly higher in iNPH than in AD patients (Figure 1e), and an optimal cut-off value of 0.303 differentiated iNPH and AD. Twenty-three (92%) iNPH and 2 (8%) AD patients had pathological BLM index ($p < 0.001$). BLM index sensitivity was 96%, specificity 92%, accuracy 94% and AUC 0.963.

DISCUSSION

In the present study, EI showed the highest AUC value compared with POR and TR. However, the highest specificity was shown by POR, and TR had the highest sensitivity.

Recently, Fällmar et al. [8] demonstrated that EI values showed the highest AUC (0.930) in discriminating iNPH from vascular dementia, progressive supranuclear palsy and multiple system atrophy, supporting the robustness of EI in the differential diagnosis between iNPH and other neurodegenerative disorders. However, although the usefulness of EI as a screening tool for iNPH patients has been reported [9], not all elderly individuals with enlarged ventricles have iNPH [10].

For this reason, some authors are proposing the use of alternative measures of ventricular enlargement or a combination of indices to improve diagnostic accuracy. POR and TR have been proposed but are still not properly investigated as useful indices for the identification of patients with hydrocephalus at risk of developing dementia [3].

Moreover, using some linear measurements of the EI, POR and TR index calculation, the BLM index was developed and was found to be able to discriminate iNPH from AD with high sensitivity (96%) and specificity (92%) using a cut-off of 0.303.

Previous studies investigated the accuracy of other neuroradiological measurements in differentiating iNPH from AD. Kim et al. [11] reported that the combination of the narrowing of the callosal angle (CA), the dilatation of the Sylvian fissure and the narrowing of superior parietal sulci could be useful in the differential diagnosis between iNPH and AD (AUC 0.89). Chan et al. [12] reported that the splenial angle presented higher accuracy than EI and CA in differentiating iNPH from AD (AUC 0.98).

Nevertheless, it should be emphasized that the evaluation of these neuroradiological features (i.e., CA, splenial angle) needs a methodological and technical expertise. In contrast, the BLM index developed does not need particular post-processing imaging software and can be executed not only on MRI but also on a computed tomography scan.

Some limits should be mentioned when interpreting our data. The relatively reduced sample size could limit the generalizability of data. Moreover, considering that our patients did not undergo shunt surgery, the diagnosis of iNPH remained "probable" and not definite. However, diagnosis was made using international guidelines and adopting a combination of clinical and radiological criteria.

In conclusion, this exploratory study confirmed the robustness of EI, supported the usefulness of POR and TR and, mostly, provided a new index, the BLM, in the differential diagnosis between iNPH and AD. Larger studies are needed to confirm our findings, to validate the BLM index and to explore its potential usefulness in the differential diagnosis between iNPH and other possible mimics.

TABLE 1 Demographic, clinical and radiological characteristics of the sample.

	iNPH ($n=25$)	AD ($n=25$)	p value
Sex, men (%)	20 (80)	15 (62.5)	0.179[a]
Age, years	74.9 ± 7.4	71.3 ± 8.6	0.147[b]
Disease duration, years	4.9 ± 3.4	3.8 ± 1.9	0.415[b]
iNPH grading scale, score	5.9 ± 1.6	–	–
MMSE, score	24.4 ± 3.6	22.8 ± 4.9	0.236[b]
FAB, score	11.5 ± 3.5	11.4 ± 3.8	0.905[a]
HAM-D, score	6.2 ± 3.9	8.6 ± 4.6	0.09[b]
RAVLT immediate recall, score	29.5 ± 6.1	24.7 ± 9.3	**0.038***,[a]
RAVLT delayed recall, score	4.9 ± 2.0	3.1 ± 2.5	**0.01***,[a]
Stroop test (s)	42.3 ± 28.5	55.1 ± 49.6	0.899[b]
Stroop test (errors)	2.3 ± 3.4	2.8 ± 4.4	0.721[b]
Phonemic verbal fluency F-A-S score	20.4 ± 9.8	19.0 ± 9.6	0.619[a]
Constructive apraxia, yes (%)	12 (48)	11 (44.8)	0.879[a]
EI	0.342 ± 0.056	0.253 ± 0.036	**<0.001***,[b]
POR	0.537 ± 0.053	0.446 ± 0.048	**<0.001***,[a]
TR	0.110 ± 0.044	0.074 ± 0.027	**0.003***,[b]
BLM	0.338 ± 0.041	0.260 ± 0.031	**<0.001***,[a]
Index parameters	**Values**	**95% confidence intervals**	
EI			
Sensitivity	80%	59.3–93.2	
Specificity	88%	68.8–97.4	
Accuracy	84%	70.9–92.8	
AUC	0.956	–	
POR			
Sensitivity	24.0%	9.4–45.1	
Specificity	100%	86.3–100	
Accuracy	62%	47.2–75.3	
AUC	0.900	–	
TR			
Sensitivity	92%	73.9–99.0	
Specificity	44%	24.4–65.1	
Accuracy	68%	53.3–80.5	
AUC	0.742	–	
BLM			
Sensitivity	96%	80.5–99.3	
Specificity	92%	75.0–97.8	
Accuracy	94%	80.7–97.8	
AUC	0.963	–	

Note: Data are expressed as mean and standard deviation or number and percentage.

Abbreviations: AD, Alzheimer's disease; AUC, area under the curve; BLM, brain linear measurement; EI, Evan's index; FAB, Frontal Assessment Battery; HAM-D, Hamilton Depression Rating Scale; iNPH, idiopathic normal pressure hydrocephalus; MMSE, Mini-Mental State Examination; POR, parieto-occipital ratio; RAVLT, Rey Auditory Verbal Learning Test; TR, temporal ratio.

*Bold values: $p<0.05$.

[a]*t* test.

[b]Mann–Whitney *U* test.

AUTHOR CONTRIBUTIONS

A.L. and G.D.: conception and design of the study, acquisition of data, analysis and interpretation of data, drafting the article. G.M.: acquisition of data, analysis and interpretation of data, revising the article critically. R.T.: analysis and interpretation of data, revising the article critically. C.E.C.: acquisition of data, analysis and interpretation of data, revising the article critically. A.N.: analysis and interpretation of data, revising the article critically. M.Z.: analysis and interpretation of data, revising the article critically, final approval of the version to be submitted. All authors approved the final version of the manuscript before submission.

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None.

CONFLICT OF INTEREST STATEMENT

The authors have nothing to declare.

DATA AVAILABILITY STATEMENT

Anonymized data not published within this article will be made available on request from any qualified investigator.

ETHICS STATEMENT

The study has been approved by the Local Ethics Review Board and has been performed in accordance with the Declaration of Helsinki and its later Statements and Declarations. A written informed consent was obtained from all the enrolled subjects.

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