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Fundoscopy as a diagnostic biomarker in idiopathic normal pressure hydrocephalus: a pilot study

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ABSTRACT

Background Idiopathic normal pressure hydrocephalus (iNPH) has a prevalence of approximately 5%. It is characterised by Hakim's triad of impaired gait, cognitive dysfunction and urinary incontinence. Despite radiological markers and liquor-dynamic tests, iNPH is difficult to diagnose due to many overlapping symptoms. The aim of this study was to evaluate funduscopy as a noninvasive method of screening patients with suspected iNPH.

Methods Patients with suspected iNPH who underwent a lumbar infusion test (LIT) were included. Funduscopy was performed before the start of the LIT, and intracranial pressure (ICP) was continually measured via lumbar cannulation. Retinal images were analysed using an artificial intelligence algorithm to determine the arteriole-venule (A/V) ratio. The A/V ratio and ICP measurements were compared with the iNPH diagnosis. In addition, the mean difference in shunt response was evaluated.

Results A significantly lower mean A/V ratio was found in the iNPH group compared with the non-iNPH group (p value: 0.02). Receiver operating characteristic curve analysis with an area under the curve of 0.75 showed a sensitivity of 88% and a specificity of 50% with an A/V cut-off of 0.86. Although not statistically significant, the mean A/V ratio was lower in the group with clinical shunt effect compared with those without (p value: 0.305).

Conclusions This study found a statistically significant difference in baseline A/V ratios between iNPH and non-iNPH groups. This pilot study suggests the A/V ratio might be able to serve as a screening tool for iNPH. If so, this would be highly beneficial for patients and could have significant medical and socioeconomic implications.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Idiopathic normal pressure hydrocephalus (iNPH) is underdiagnosed, leading to cognitive decline and functional impairment. Current diagnostic methods are invasive and imprecise, resulting in some patients missing treatment while others undergo ineffective shunt surgery.

WHAT THIS STUDY ADDS

⇒ Fundoscopy-based A/V ratio analysis significantly differentiates iNPH from non-iNPH patients, showing high sensitivity (88%). This suggests funduscopy could be a noninvasive screening tool to improve diagnosis.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ If validated, funduscopy could enable earlier diagnosis, prevent unnecessary surgeries and ensure timely treatment, reducing cognitive decline and optimising healthcare resources.

BACKGROUND

Idiopathic normal pressure hydrocephalus (iNPH) is a neurological condition characterised by Hakim's triad of impaired gait, cognitive dysfunction and urinary incontinence.[1–3] iNPH predominantly affects the older population and has an estimated prevalence of 5.9% among people aged >80 years[4] and 3.7% among people aged >65 years.[5] It was first described in 1965 by Hakim and Adams and has since been acknowledged as a partly reversible type of dementia.[6]

Despite extensive research, there is still no consensus on the underlying pathophysiology of iNPH. The development of iNPH may be related to an imbalance between cerebrospinal fluid (CSF) production and absorption.[7] Among other pathophysiological theories, it has been proposed that iNPH may primarily stem from underlying vascular disease[8] that results in ventricular dilation due to decreased vascular compliance and increased pulsation in the distal capillaries and veins.[9] The presence of periventricular oedema and the high prevalence of vascular diseases in iNPH patients further supports the notion of an underlying vascular component.[10] Impaired granular absorption, potentially caused by alterations of the venous sinuses, could be another significant factor in the development of iNPH.[11]

The limited sustained effect of shunting iNPH patients, typically 5–7 years,[12] suggests that iNPH is more complex than a simple imbalance between CSF production and absorption. A systematic review revealed that only 70–80% of iNPH patients experience objective improvement following shunt surgery.[13] This variability could possibly be due to several factors, including diagnostic challenges, delay of surgery, patient comorbidity and disease progression. The heterogeneity observed in multiple systematic reviews[13–15] underlines the difficulty in diagnosing and treating iNPH patients in a timely manner, likely due to the many overlapping symptoms—and even in classifying the disease itself.

It is estimated that 9–14% of residents in assisted-living and extended-care facilities have iNPH.[16] A Norwegian study showed that the incidence of shunted iNPH patients was significantly lower than the incidence of probable iNPH, suggesting that the condition is severely underdiagnosed and undertreated.[17] The cost in 2015 of the estimated 60 522 undiagnosed shunt-responsive patients in the European Union was estimated to be nearly €330 million.[14] As early treatment can improve outcomes of shunt surgery and increase survival rates,[18] the development of a new screening method for early detection of iNPH would greatly benefit patients, their families and society.

Previous studies have suggested that noninvasive intracranial pressure (ICP) can be estimated by the arteriole-venule (A/V) ratio obtained through funduscopy.[19–22] The A/V ratio has been proposed as a surrogate marker of intracranial compliance and vascular resistance, potentially reflecting impaired cerebral autoregulation and/or elevated ICP. Although only four studies to date have explored this relationship[19–22]—and none in iNPH patients—initial findings suggest that the A/V ratio may hold diagnostic value. However, the existing evidence is sparse, and the clinical utility of the A/V ratio in distinguishing iNPH from non-iNPH patients remains uncertain. Its potential to predict shunt responsiveness also warrants further investigation. Further research is needed to clarify its role as a diagnostic biomarker in an outpatient setting. This study aims to address these gaps of knowledge.

The present study was conducted as an explorative pilot study with the hypothesis that patients with iNPH have compromised brain compliance, which can be visualised by dynamic retinal vessel funduscopy. Based on the experience from previous studies,[19–22] the aim of this study was to investigate whether assessment of retinal vessels through funduscopy could distinguish iNPH patients from non-iNPH patients. The specific objectives were to (i) assess whether A/V ratio and intracranial pressure measurements were statistically significantly different between iNPH and non-iNPH groups, (ii) use receiver operating characteristic (ROC) curve analysis to evaluate the diagnostic performance of the A/V ratio in identifying patients with iNPH and to determine the optimal cut-off value for the A/V ratio, (iii) calculate sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) to assess the diagnostic accuracy of A/V ratio in identifying iNPH patients and (iv) investigate whether the mean A/V ratios could differentiate shunt responders from nonresponders.

METHODS

Study participants

We initially included 50 patients with suspected iNPH who were seen at the neurosurgical outpatient clinic at Odense University Hospital, Denmark, and underwent a lumbar infusion test (LIT). Informed written consent was obtained from all patients prior to data collection. The study was approved by the Regional Committee on Health Research Ethics for Southern Denmark (S-20170038).

Diagnostic workup

The diagnosis of iNPH was based on a combination of clinical, radiological and CSF dynamic assessments. All patients underwent standardised clinical evaluation, including assessment of gait, urinary continence and cognitive function. Gait was specifically evaluated for characteristic features of iNPH such as a magnetic and shuffling pattern. Cognitive function was assessed using the Mini-Mental State Examination, and patients were asked to self-report urinary incontinence. A diagnosis of iNPH required the presence of impaired gait in combination with at least one additional symptom from Hakim's triad.

Radiologically, all patients underwent brain imaging (CT or MRI) and were evaluated for features of disproportionately enlarged subarachnoid space hydrocephalus (DESH).[23] While no strict DESH score threshold was applied, the presence of key radiological markers—particularly a sharp callosal angle and tight high convexity sulci—was considered essential supportive findings[24]

Following clinical and radiological assessment, a LIT was performed in all patients. The test was considered positive if the resistance to outflow (Rout) was greater than 12 mmHg/mL/min. If the clinic and/or radiology was not consistent with a positive LIT, a tap test (TT) was performed. A net volume of 30–50 mL CSF was extracted. In cases where Rout was borderline (10–12 mmHg/mL/min), or in selected patients with lower Rout values but suggestive clinical and radiological findings, a TT was performed at the discretion of the treating neurosurgeon. TT response was evaluated 1 week after the procedure based on symptom improvement reported by the patient and their next of kin.

Patients were offered ventriculoperitoneal shunting if they demonstrated clinical improvement following the TT or had a clearly positive LIT in conjunction with supportive clinical and radiological findings. Patients with both a negative LIT and no effect of the TT were not offered a shunt and were classified as non-iNPH.

Funduscopy and ICP measurement

For this study, funduscopy was performed with the patients in a supine position after the lumbar puncture

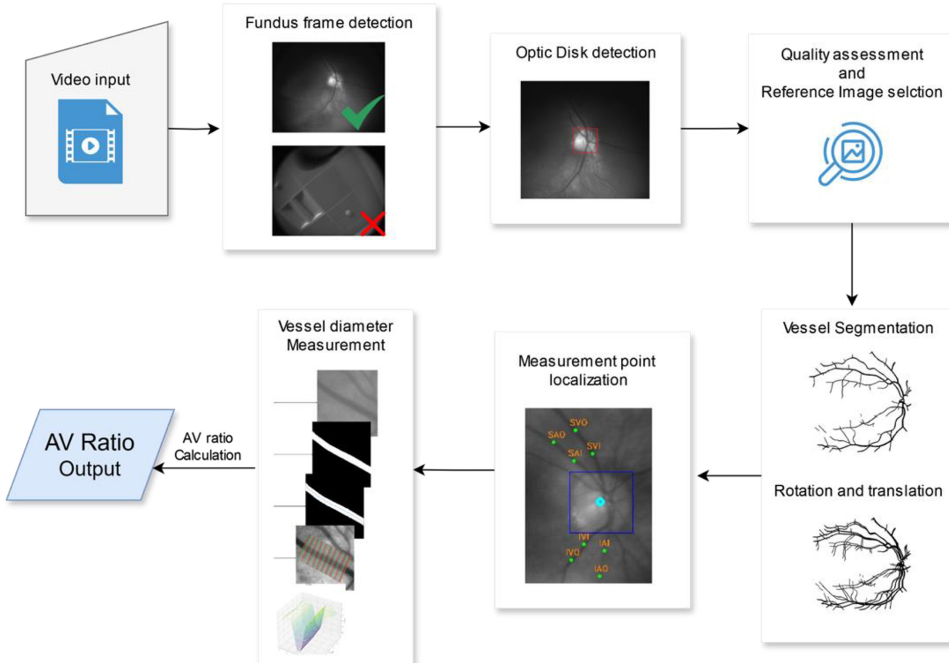

Figure 1 Workflow for A/V ratio calculation from fundus videos. Key steps included frame selection, optic disc detection, quality assessment, vessel segmentation and alignment, measurement point localisation, vessel diameter measurement and final A/V ratio calculation. A/V, arteriole-venule.

and before the initiation of the LIT. Patients were lying on their left side as the needle was placed. After needle placement in the lumbar subarachnoid space, baseline ICP was obtained from LiqouGuard 7 (Möller Medical GmbH, Fulda, Germany). Before saline infusion, funduscopy was performed on the right eye only due to the patient's position. The method for obtaining funduscopy images was similar to the method used in previous studies by our group.[19 20] In parallel with funduscopy, ICP was continuously recorded from LiqouGuard 7 (Möller Medical GmbH, Fulda, Germany) with a webcam. The mean ICP was calculated from a period of 20 s of the webcam video obtained time matched in parallel with the funduscopy.

Funduscopy video analysis and A/V ratio computation

The algorithm processes fundus videos captured by handheld fundus cameras, combining traditional image processing techniques with advanced machine learning models. Each of the machine learning models was trained using validated data from a large database of images containing over 100 000 fundus images. The following stepwise method description is illustrated in figure 1. This method has been described in detail previously.[20]

Fundus frame detection

The frames of each video were processed by a deep learning model to identify valid fundus frames containing the optic disc, filtering out nonrelevant frames.

Optic disc detection

Once valid frames were identified, object detection was applied to detect the exact location and size of the optic disc. This information serves as a fixed anatomical reference for the subsequent image-processing tasks.

Quality assessment and reference frame selection

The quality of each valid frame was graded,[25] and the frame with the highest quality was selected as reference. Quality scores were generated to confirm the reliability of the data.

Vessel segmentation and image alignment

Vessel segmentation was applied on the fundus frames, and segmented vessels were used to accurately align the frames by detecting and tracking vessels. Using the reference frame as a guide, all other frames were rotated and translated to ensure consistent alignment of the vessels across the video sequence. The optic disc was the central reference point for this process.

Measurement point localisation

The algorithm identifies eight key measurement points—four on arteries and four on veins—at specific distances from the optic disc margin: 0–0.5 and 0.5–1 optic disc diameters.[26 27] These predefined locations ensure consistency in measuring vessel diameters across patients and video frames.

Vessel diameter measurement

The vessel diameters were measured using an automated artificial intelligence (AI) algorithm for vessel width from StatuManu ICP ApS (Glostrup, Denmark), which combines a vessel segmentation obtained with deep learning, skeletonisation, drawing perpendicular intensity profiles and edge detection using decay points.[28]

A/V ratio calculations

In the final step, the A/V ratio for each artery-vein pair was calculated by taking the weighted median of each artery and vein diameter across the video. These median values were then used to compute the A/V ratio.

The patients were divided into two groups (iNPH or non-iNPH) based on the outcome of the above-mentioned criteria and tests. Patients who met the diagnostic criteria for iNPH were subsequently offered a ventriculoperitoneal shunt.

Blinding

The diagnostic classification of the individual patients as iNPH or non-iNPH was based on clinical symptoms, imaging findings and CSF dynamics determined prior to A/V ratio analysis. This diagnostic information was subsequently provided to the research team using coded study ID numbers. The A/V ratio was calculated by Statumanu (Glostrup, Denmark) using an automated AI-based algorithm, without access to clinical data. Final statistical analyses were conducted only after both clinical groupings and A/V data were available, using anonymised datasets. No investigator involved in diagnosis had access to the A/V ratio during patient evaluation, and no individual involved in A/V processing had access to diagnostic or outcome data, ensuring effective blinding throughout the study.

Statistical considerations

A Q-Q plot was generated to evaluate the normality of the data for both the A/V ratio and ICP measurements (online supplemental figure 1).

Two-tailed t-tests were used to investigate whether the A/V ratio and the ICP were statistically significantly different between the iNPH group and the non-iNPH group. ROC curve analysis was undertaken to evaluate the diagnostic performance of the A/V ratio in identifying patients with iNPH and to determine the optimal cut-off value for the A/V ratio. The sensitivity, specificity, PPV and NPV were calculated to assess the diagnostic accuracy of the A/V ratio in identifying iNPH patients. The mean A/V ratio was also analysed in relation to clinical response to shunting. Only patients who received a shunt were included in this analysis. Although 16 patients were initially classified in the iNPH group, a subsequent data correction revealed that one patient had not received a shunt and was therefore excluded from the effect analysis, leaving 15 patients. Despite this, the patient remained classified as iNPH due to a DESH score of 8, magnetic and shuffling gait, cognitive impairment and a Rout of 12 mmHg/mL/min, but with no effect after TT. Shunt response was assessed based on clinical documentation in the patient's medical record, specifically the clinician's evaluation approximately 1 month after surgery. Gait improvement was the primary parameter of interest and was consistently documented. A Wilcoxon rank-sum test was used to compare the A/V ratio between patients with and without observed shunt effect.

All statistical analyses were performed using Python and a significance level was set at $p<0.05$. Given the exploratory nature of this pilot study, power calculations were not conducted prior to study initiation.

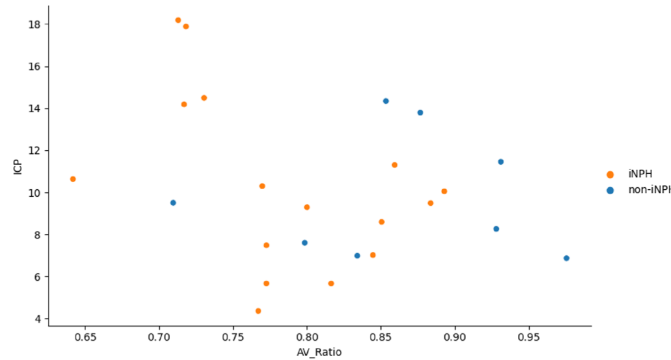

Figure 2 Distribution of baseline A/V ratios from all 24 patients relative to ICP prior to infusion test and tap test for patients later diagnosed with iNPH or without iNPH (non-iNPH). A/V, arteriole-venule; ICP, intracranial pressure; iNPH, idiopathic normal pressure hydrocephalus.

RESULTS

Of the 50 patients enrolled in this study, 26 had insufficient image quality to calculate the A/V ratio. Thus, only 24 patients met the criteria for inclusion in the final data analysis. Of these, 16 patients were diagnosed with iNPH, and 8 patients were categorised as non-iNPH. The

Table 1 Demographic and clinical data for patients diagnosed with iNPH and those without iNPH (non-iNPH)

Variable (n=24)	iNPH (n=16)	Non-iNPH (n=8)	P value
Sex (M/F)	9/7	6/2	0.66
Mean age, years (SD)	73.3 (5.7)	76.9 (2.6)	0.05
Mean BMI, kg/m^2 (SD)	28.3 (3.2)*	26.1 (5.0)*	0.28
Hypertension, n (%)	14 (88%)	8 (100%)	0.54
Hypercholesterolaemia, n (%)	11 (69%)	5 (63%)	1.00
Diabetes type 2, n (%)	5 (31/%)	1 (13%)	0.62

*BMI data were missing for one patient in the iNPH group and for two patients in the non-iNPH group.
BMI, body mass index; iNPH, idiopathic normal pressure hydrocephalus.

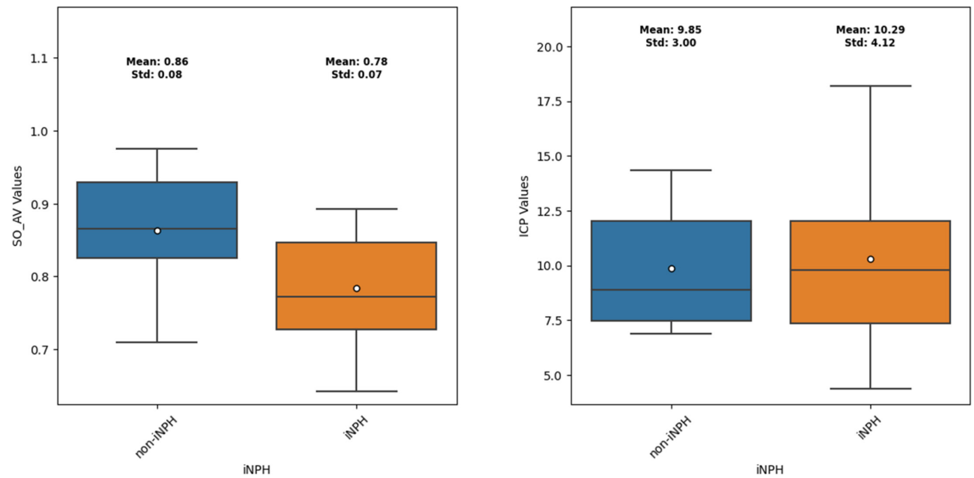

Figure 3 Box plots showing the mean A/V ratio and mean ICP obtained prior to the initiation of the infusion test. A/V, arteriole-venule; ICP, intracranial pressure.

demographic and clinical data for these 24 participants are presented in table 1.

Figure 2 illustrates the distribution of initial A/V ratios on the X-axis and ICP on the Y-axis prior to infusion test and TT.

The mean A/V ratio was 0.78 (SD: 0.07) in the iNPH group compared with 0.86 (SD: 0.08) in the non-iNPH group (figure 3). A two-tailed t-test indicated a statistically significant difference between the groups (p=0.02). The two groups had similar baseline ICP values: 10.29 mmHg (SD: 4.12) for the iNPH group and 9.85 mmHg (SD: 3.00) for the non-iNPH group (figure 3). A two-tailed t-test on the ICP data yielded a nonsignificant p value of 0.8.

ROC curve analysis

The area under the curve (AUC) was 0.75 (figure 4). An optimal A/V ratio cut-off of 0.86 yielded a high sensitivity of 0.88, that is, it would correctly identify 88% of iNPH patients, but had a specificity of 0.50, that is, indicating a 50% false-positive rate. The PPV was 0.78, meaning 78% of those testing positive were true iNPH patients, while the NPV was 0.67, indicating 67% of those testing negative were true non-iNPH patients.

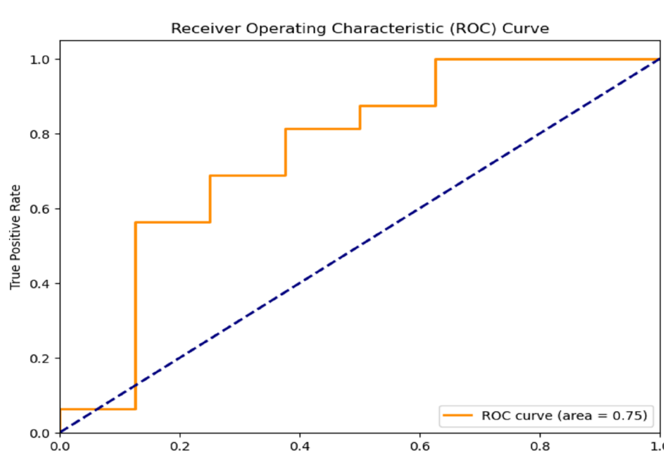

Figure 4 Receiver operating characteristic curve showing the ability of the A/V ratio to distinguish patients with iNPH from patients without iNPH. A/V, arteriole-venule; iNPH, idiopathic normal pressure hydrocephalus.

Comparison of A/V ratio and ICP by shunt effect

To explore whether the A/V ratio and ICP were associated with clinical response to shunting, we conducted a subgroup analysis of the 15 patients who had received a ventriculoperitoneal shunt. Of these, 13 patients experienced a clinical effect from the shunt, while 2 did not.

The mean A/V ratio was lower in patients who experienced a positive shunt response (mean: 0.7857, SD: 0.0621) compared with those without effect (mean: 0.8476, SD: 0.0041). Due to the low number of cases, this difference was not statistically significant (p value: 0.305). However, the trend suggests a possible association between the lower A/V ratio and favourable clinical outcomes.

The mean ICP was not statistically significantly different between the two groups (table 2).

DISCUSSION

This pilot study investigated the diagnostic potential of the A/V ratio as a noninvasive biomarker for iNPH. ROC curve analysis showed that the A/V ratio had a diagnostic accuracy with an AUC of 0.75, a sensitivity of 88% and a specificity of 50%. While the moderate specificity reflects the false-positive rate, the high sensitivity with a high PPV

Table 2 Mean A/V ratio and ICP values with corresponding p values

Group	A/V ratio mean (SD)	ICP mean (SD)	N
No effect	0.8476 (0.0041)	13.50 (2.12)	2
Effect	0.7857 (0.0621)	9.77 (4.26)	13
Total	0.7939 (0.615)	10.29 (4.12)	15
p-value	0.305	0.308	

A/V, arteriole-venule; ICP, intracranial pressure.

of 0.78 indicates that the A/V ratio has potential as an initial screening measure that could help differentiate iNPH from other neurodegenerative diseases with overlapping clinical features.

Current diagnostic tests for iNPH, specifically the LIT and the TT, have various limitations, are invasive and carry procedural risks.[29] While the LIT and TT show widely variable sensitivity and specificity, the A/V ratio offers promise as a noninvasive addition to iNPH diagnostics. Reported TT sensitivity ranges from 26 to 87%, with a specificity from 33 to 100%,[30] while LIT has demonstrated a sensitivity of 70% but a lower specificity of 35%.[31] These limitations highlight the need for supplementary reliable markers in iNPH diagnosis, and the A/V ratio appears to be comparable to or better than these current diagnostic methods. Both tests carry a considerable risk of false-negative results and should be regarded as supportive, provocative tools rather than definitive diagnostic measures. While combining the TT and LIT may help reduce the false-negative rate,[32] other studies have suggested that combining the two does not significantly improve predictive accuracy.[31] This emphasises the need for more reliable and objective biomarkers to guide patient selection for shunt surgery.

Distinguishing iNPH from other forms of dementia is crucial as patients with dementia typically have poorer outcomes after shunt surgery compared with those with mild or no cognitive deficits.[33] The high PPV of the A/V ratio (0.78) suggests that it could serve as an initial screening measure to better identify true iNPH cases, thereby reducing unnecessary surgical interventions in patients unlikely to respond to shunting. This is supported by the statistically significant mean difference in the A/V ratio between the iNPH and non-iNPH groups (p=0.02).

In this study, we observed a statistically significant mean difference in the A/V ratio between the iNPH and non-iNPH groups (p=0.02). Interestingly, this difference could not be attributed to mean ICP, as no significant differences were found between the groups (p=0.8). These findings align with earlier studies linking the A/V ratio to compromised brain compliance, a key pathophysiological factor in iNPH. For example, Rodriguez *et al* and Qvarlander *et al* demonstrated that pulse pressure amplitudes and the rate of ICP increase are more predictive of shunt response in iNPH, rather than absolute ICP.[34 35] Such compromised compliance likely affects ocular haemodynamics, contributing to the observed differences in the A/V ratio. In iNPH, cerebral venous pressure is believed to increase, possibly as a result of reduced intracranial compliance, which may contribute to the development of hydrocephalus.[36] Over time, this elevated venous pressure can lead to venular dilation due to impaired drainage, and this mechanism might explain the lower mean A/V ratio observed in the iNPH group. It is also important to consider the anatomical course of retinal venous drainage. Venous blood from the retina flows through the central retinal vein, which travels within the optic nerve sheath and drains into the superior and inferior ophthalmic veins.[37] These veins then connect to the cavernous sinus, continue through the petrosal sinuses, then the sigmoid sinuses and ultimately exit the skull via the jugular vein through the jugular foramen.[38] In contrast, the increase in venous pressure described by Bateman occurs in the superficial cerebral venous system, which drains via the superior sagittal sinus.[36] For this increased pressure to influence the retinal veins, it would need to propagate throughout the interconnected venous system. This anatomical separation may reduce the ability of the A/V ratio to predict shunt responsiveness in iNPH.

To assess whether the A/V ratio could also reflect clinical response to shunting, we performed a subgroup analysis comparing shunt responders with nonresponders. While the difference in mean A/V ratio was not statistically significant (p=0.305), patients who benefited from shunting tended to have lower A/V ratios. This finding is consistent with our primary analysis, in which iNPH patients had significantly lower A/V ratios than non-iNPH patients. Given the very small number of nonresponders (n=2), the analysis is limited by low statistical power, probably explaining the lack of statistical significance. Nonetheless, the observed tendency may support the hypothesis that the reduced A/V ratio is associated with compromised brain compliance and shunt responsiveness.

Future studies are needed to validate these findings and assess the value of integrating the A/V ratio into existing diagnostic workflows for iNPH in larger cohorts. Our exploratory analysis suggests a trend towards lower A/V ratios in shunt responders, indicating potential as a predictor of treatment response. If confirmed, the A/V ratio could support both diagnosis and patient selection. A key limitation is the use of retrospective, nonstandardised tests and subjective assessments to define shunt and TT effect. Prospective studies using standardised outcome measures and improved fundus imaging are needed to enhance diagnostic accuracy and clinical applicability. In addition, our planned future and larger prospective studies will address the question of which standard NPH diagnostic marker best correlates with the A/V ratio.

CONCLUSION

Current diagnostic tests for iNPH have limitations, emphasising the need for further research to refine the diagnostic process. The results of this explorative study suggest that the A/V ratio has potential as a biomarker, which may supplement or improve on current diagnostic methods as it offers a noninvasive measure of brain compliance in iNPH. Future investigations should aim to further validate this method across larger cohorts and with improved imaging technology.

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Contributors MJN, MCSA and FRP planned the project. The organisation and data collection were performed by MJN. The statistical analysis was performed by MJN and StatuManu ICP ApS. The data were interpreted by MJN, NLE, MCSA, ETN, SM, CBP and FRP. Preparation and creation of the original draft of the article was performed by MJN, and all authors commented on previous versions of the manuscript. The manuscript was reviewed, edited and accepted by MJN, NLE, MCSA, ETN, SM, CBP and FRP. MJN is the guarantor. He has used ChatGPT for grammar corrections.

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Competing interests MJN has received funding from StatuManu ICP ApS for his PhD and undergraduate project and worked as a medical consultant for the company for 6 months. MCSA received partial funding from StatuManu ICP ApS for his PhD. NLE received funding from StatuManu ICP ApS for his undergraduate project.

Patient consent for publication Consent obtained directly from patient(s).

Ethics approval This study involves human participants and was approved by the Regional Committee on Health Research Ethics for Southern Denmark (S-20170038). Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. The study data are available from StatuManu ICP ApS, but restrictions apply as the data were used under license for the current study and are not publicly available. Data may be requested from the authors upon reasonable request and with permission from StatuManu ICP ApS. The following authors can be contacted: Mathias Just Nortvig (mathias.just.nortvig@rsyd.dk), Mikkel Schou Andersen (mikkel.c.schou.andersen@rsyd.dk) or Frantz Rom Poulsen (frantz.r.poulsen@rsyd.dk).

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