Noninvasive Transorbital Assessment of the Optic Nerve Sheath in Children: Relationship Between Optic Nerve Sheath Diameter, Deformability Index, and Intracranial Pressure

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Title:
Non-invasive transorbital assessment of the optic nerve sheath: relationship between optic nerve sheath diameter, deformability index and intracranial pressure

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Abstract

Background: Measurement of optic nerve sheath diameter (ONSD) is a promising technique for non-invasive assessment of intracranial pressure (ICP), but has certain limitations. A recent study showed that the Deformability Index (DI), a dynamic parameter quantifying the pulsatile nature of the optic nerve sheath (ONS), could differentiate between patients with high versus normal ICP.

Objective: This study aimed to further evaluate the diagnostic accuracy of the DI, when interpreted together with ONSD.

Methods: This prospective study included children undergoing invasive ICP measurement as part of their clinical management. Ultrasound images of the ONS were acquired prior to measuring ICP, the images were further processed to obtain the DI. Patients were dichotomized into high (≥ 20 mmHg) or normal ICP groups and compared using the Mann-Whitney U-test. Diagnostic accuracy was described using area under the ROC curve (AUC), sensitivity and specificity, correlation between DI, ONSD and ICP was investigated using linear regression.

Results: 28 patients were included (19 high ICP). The DI was lower in the high ICP group (0.105 versus 0.28, p=0.001). AUC was 0.87, and a cut-off value of DI≤0.185 demonstrated sensitivity of 89.5% and specificity of 88.9%. Diagnostic accuracy improved when combining DI with ONSD (AUC 0.98, sensitivity 94.7%, specificity 88.9%) and correlation with ICP improved when combined analysis of DI and ONSD was performed (Pearson correlation coefficient: 0.82 versus 0.42, respectively, p=0.012).

Conclusion: The DI was significantly lower for patients with high versus normal ICP. This relationship improved further when the DI and ONSD were interpreted together.

Introduction

Assessment of intracranial pressure (ICP) remains a cornerstone of management of patients with suspected neurological disorders. Invasive methods remain the criterion standard for ICP monitoring in most clinical scenarios, but are limited by cost, availability and the associated risk of infection and hemorrhage.[1] A reliable, accurate and reproducible non-invasive method for assessing ICP is therefore warranted. While a number of non-invasive techniques have been described, none has demonstrated acceptable diagnostic accuracy as a surrogate marker of absolute ICP.[2,3]

The eye and visual system have been described as potential surrogate markers of pathology in patients following traumatic brain injury (TBI).[4-6] Measurement of the optic nerve sheath diameter (ONSD) specifically, has revealed a good relationship with increasing ICP in a number of conditions in adults and in children.[7-11] While this technique appears promising, accuracy remains limited due to variation in reported cut-off values.[12] Padayachy et al (2016) proposed that the dynamic, pulsatile properties of the optic nerve sheath (ONS) were influenced by ICP, specifically that the ONS appears stiffer due to the increased amount of cerebrospinal fluid (CSF) within the sheath as ICP increases.[13] These dynamic properties were investigated using transorbital ultrasound images to study the response of the ONS to cardiovascular pulsation. A quantitative parameter called the Deformability Index (DI) was introduced, and found to be significantly lower for patients with high ICP compared to patients with normal ICP. However, due to the exploratory nature of the study, data were analysed retrospectively, and the ultrasound acquisition was not fully standardized. Furthermore, the study was limited by a relatively small sample size.

The present study therefore aimed to address some of these shortcomings by analysing prospectively collected data to further investigate the diagnostic accuracy of both the DI and ONSD independently, as well as the combination of the two parameters compared to invasively measured ICP as the reference standard.

Methods

Participants

This prospective study included children undergoing invasive ICP measurement as part of their clinical management. Patients (between the ages of 1 and 14 years) who underwent a neurosurgical procedure involving invasive ICP monitoring were eligible for inclusion in the study.

Exclusion criteria:

- Children with an open fontanelle
- Patients with documented ocular or orbital pathology, e.g. orbital trauma or cataract, which would preclude sonographic evaluation of the ONS
- Patients with signs of critically raised ICP, needing urgent surgery;
- Patients who were hemodynamically unstable between ONSD acquisition and ICP measurement
- Patients receiving medication that would decrease ICP between ultrasound imaging and ICP measurement, i.e. mannitol, hypertonic saline or steroids
- Time between ultrasound imaging and ICP measurement exceeded 1 hour.

Further, due to constraints in the processing method used to calculate the DI, datasets with less than 5 seconds continuous stable acquisition (i.e. limited hand motion) were excluded. Each dataset was reviewed after acquisition, but before processing. For some patients, this meant that data from one eye only was used for calculation of the DI.

Informed consent was obtained for all patients included in the study, and approval was obtained from the institutional human ethics committee.

Data acquisition

Ultrasound imaging of both eyes was performed using a linear array probe (L15-7io) attached to an IU-22 ultrasound scanner (Philips, Bothell, USA). Imaging was done after patients had undergone anaesthetic induction and were being mechanically ventilated, hemodynamically stable and prior to insertion of the ICP monitor. All

patients were positioned supine with the head central and elevated to approximately 30 degrees. A clear film protective dressing was placed over both eyes to protect the globe from any potential injury. A layer of coupling gel was applied over the closed upper eyelid. Positioning of the probe over the eye was always carefully performed. This process included use of the middle finger and left hand to palpate the bony surface of the superior orbital rim, glabella and inferior orbital rim, to ensure that the application of the probe over the surface of the eyelid never exerted any pressure on the globe itself. The acquisition was made with as little motion as possible.

ONSD measurements were acquired at an angle perpendicular to the optic nerve and at a depth of 3 mm posterior to the lamina cribrosa of the sclera. All acquisitions were performed by a single operator and measurements were performed using the digital calliper tool on the ultrasound machine. Pulse rate was registered concurrently with the ultrasound acquisition.

ICP measurement was performed by insertion of a parenchymal microsensor (Codman®) or a ventricular catheter.

Data processing

This technique was based on the hypothesis that raised ICP leads to increased stiffness of the ONS complex through accumulation of CSF, thus reducing its ability to deform under cardiovascular pulsation. The Deformability Index (DI) was calculated according to the method described by Padayachy et al (2016), which estimates the magnitude of motion (D_1 and D_2) in the lateral direction on both sides of the ONS over the cardiac cycle. [13] The dimensionless parameter DI quantifies the deformation of the nerve sheath complex according to the formula:

$$DI = \frac{|D_1 - D_2|}{D_1 + D_2} \quad (1)$$

The method depends on manual initialization of two points. To reduce operator dependency, the initialization was standardised by drawing a central, straight line through the optic nerve axis, with perpendicular measurements of the DI at pre-

defined depths from the sclera (Fig 1). Results from 3.0 mm, 3.5 mm and 4.0 mm depth were calculated and average values were used in the further analysis.

For patients where ultrasound acquisitions from both eyes were included, the average of left and right eye was calculated and used as the value for DI in the further analysis.

Statistical analysis

Patients were dichotomized into high and normal ICP groups, with high ICP defined as ICP $\geq$ 20 mmHg. Descriptive values were reported using median and interquartile range (IQR) for ICP, DI and ONSD. The one-sided Mann-Whitney U test was used for comparison between the two groups (significance level $p < 0.05$). Analyses were done for both DI and ONSD individually, as well as for a linear combination of these two parameters.

Diagnostic accuracy was expressed by the area under ROC curve (AUC), as well as sensitivity and specificity given the optimal cut-off for our material. 95% confidence intervals (95% CI) were included for all measures of diagnostic accuracy.

Further, linear regression was calculated for ICP versus DI and ONSD individually, and for the combination of DI and ONSD using multivariable regression. Pearson correlation coefficients (with 95% CI) were reported, and p values were calculated using F statistic versus constant model. Fisher exact test was used for association between DI and ONSD, and the Fisher transformation for comparison of correlation coefficients.

Results

Participants

The study included 28 patients, with a median age of 30 months (IQR: 22 to 60). 19 patients had high ICP (median 26 mmHg, IQR: 24 to 29) and 9 had normal ICP (median 15 mmHg, IQR: 9 to 18). Demographic details are included in Table I.

Sufficiently stable ultrasound sequences were acquired from both eyes in 20 patients, and for one eye only in eight patients.

Diagnostic accuracy of the Deformability Index and the ONSD

The deformability index for the high ICP group was 0.105 (IQR: 0.08 to 0.13) versus 0.28 (IQR: 0.22 to 0.35) for the normal ICP group ($p = 0.001$). ROC analysis demonstrated an area under curve (AUC) of 0.87. Choosing a cut-off value for DI between 0.17 and 0.21 resulted in sensitivity of 89.5% and specificity of 88.9%.

The ONSD in the high ICP group was 6.0 mm (IQR: 5.8 to 6.4) versus 5.5 (IQR: 4.8 to 5.77) for the normal ICP group ($p = 0.002$). AUC was 0.84. Optimal cut-off was 5.61 mm, resulting in sensitivity of 94.7% and specificity of 77.8%.

Both DI and ONSD for each patient are included in Table I. Boxplots and ROC curves are shown in Fig 2 and Fig 3, respectively.

Both the DI and the ONSD were independently correlated with ICP. Pearson correlation coefficients were -0.72 ($p < 0.0001$ versus constant model) for DI and 0.42 ($p = 0.026$ versus constant model) for the ONSD. Although the observed correlation in our data was stronger for the DI than for the ONSD, we could not conclude that the difference was significant ($p = 0.10$). Scatter plots with regression lines are included in Fig 4.

Although there was a clear association between DI and ONSD ($p=0.011$), there was no significant linear correlation between the two (Pearson correlation coefficient -0.05, $p=0.79$).

Multivariable regression including both DI and ONSD

By combining both the DI and the ONSD in a multivariable regression model, the optimal multivariable regression formula was

$$ICP = 4 + 4.3 \cdot ONSD\text{-}42 \cdot DI \quad (2)$$

The combined diagnostic information gave an AUC of 0.98. Using estimated ICP ≥ 20 mmHg as positive cut-off, the sensitivity was 94.7% and the specificity 88.9%.

The Pearson correlation coefficient between measured and estimated ICP was 0.82 ($p < 0.001$). The combination of DI and ONSD showed significantly better correlation to ICP compared to ONSD alone ($p=0.012$), but was not significantly improved compared to the DI alone based on our data ($p=0.38$).

2x2 contingency tables are included in Table II. AUC, sensitivity, specificity and Pearson correlation coefficients, along with their 95% confidence intervals, are summarized in Table III.

Discussion

The purpose of the current study was to prospectively analyse the validity of the DI as a surrogate marker of ICP, and to investigate the benefit of a combined analysis of the DI and ONSD.

Our study demonstrated a significant difference in the DI between the groups with high versus normal ICP. The results suggest that the DI could be used as an independent diagnostic marker of raised ICP with nearly 90% sensitivity and specificity.

Both ONSD and DI demonstrated good diagnostic accuracy independently. Although statistical significance could not be inferred based on our data, the combination of these two parameters may provide an even stronger diagnostic marker. The correlation with ICP also appeared to be better for DI than for ONSD, and best when combining the two parameters.

Most studies comparing ONSD measurement to clinical assessment or imaging-based evidence of raised ICP have used 5.0 mm as a default cut-off value for predicting raised ICP, with variable diagnostic accuracy.[14-16] The reported ONSD cut-off values however, range from 4.1-5.9 mm.[16-21] Studies using an ICP threshold of 20 mmHg, describe ONSD cut-off values between 4.8 and 5.9 mm.[22] The variable diagnostic accuracy reflects the difficulty regarding optimal ONSD cut-off values for detecting raised ICP. The variation in individual baseline measurements and the difficulty in estimating the distensibility of the ONS are perhaps the two most significant factors responsible for the poor specificity of this technique.[21] It is to this end that a number of laboratory-based studies have investigated the dynamic and biomechanical properties of the optic nerve sheath complex.[23-30]

In a previous paper involving a different set of data obtained from 15 paediatric patients, the DI for left and right eyes was reported separately.[13] When revisiting the data from the previous study and calculating the average of the DI for the left and right eyes, we found an optimal positive cut-off value of DI≤0.185. Further, median

DI for the high and normal groups was 0.11 (IQR: 0.075 to 0.1175) versus 0.24 (IQR: 0.195 to 0.31), respectively ($p<0.001$). The values obtained in the current study agree well with these prior data, and the technique therefore appears to be reproducible, also with prospectively collected data from a higher number of patients. A meta-analysis is provided in Table IV.

Limitations of the study include the fact that this is a paediatric cohort, which restricts widespread application of the findings. While inter-rater variability testing would be helpful, measurement of the DI is largely automated using the software analysis (described previously) and non-invasive ICP assessment does not yet provide the option for continuous monitoring.

The value of analysing the dynamic pulsatile properties of the ONS is best appreciated when the results are interpreted together with the static ONSD measurement. The benefit of this approach lies in the added information that dynamic imaging provides. This is specifically useful as the ONSD measurement may vary in individuals. A widened ONSD in some may merely represent the upper limit of normality, whereas in others it may be consistent with raised ICP. The stiffness of the ONS in such cases would be essential in differentiating normal variants from pathological cases. While both the ONSD and DI measurements demonstrate a close relationship with ICP, performing a regression analysis combining both parameters appears to improve the diagnostic accuracy. This could reinforce the assertion that the diameter and stiffness of the ONS should be analysed together in order to best appreciate changes in the morphological and anatomical features associated with increasing ICP. The distinct benefit of this approach addresses a recurring shortcoming described in measuring the ONSD as a standalone marker of ICP, i.e. the individual variability and subsequent variation in the best cut-off value to predict abnormally raised ICP. [22]

The early work done by Hansen and Helmke (1997) described a clear relationship between ICP and CSF distension of the ONS.[7] The biomechanical behaviour of the ONS has however always been quite difficult to define and quantify. This characteristic of the ONS likely accounts for the vast majority of the variability described in the literature. This work therefore addresses a fundamental issue in

analysing the ONS. The additional benefit of describing the morphology of the optic nerve head, sheath and nerve in finer detail, combined with analysis of blood flow changes using Doppler flowmetry, could only serve to further refine the technique of using the visual system as a marker of raised ICP.

Conclusion

A significant difference in DI was noted between patient groups with high versus normal ICP. Sensitivity and specificity of almost 90% indicate that the deformability index is a valid non-invasive marker of raised ICP. Combining the DI with ONSD measurement provides additional information and could improve the diagnostic accuracy of ONS assessment as a surrogate marker of raised ICP.

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Figure legends

Fig 1. Transorbital ultrasound. Posterior part of the globe indicated by yellow curve, optic nerve (ON) by stippled, yellow square. Initialization was guided by the red dotted line vertical through the ON. The tissue motion was tracked in three different depths from the posterior part of the globe, indicated by red marks. The white circles illustrate the centre of tracking region for 3.5 mm depth.

Fig 2. Boxplots illustrating median and spread. Left: intracranial pressure (ICP), mid: optic nerve sheath diameter (ONSD), and right: Deformability Index (DI). The plots show median (horizontal lines) and the interquartile range (IQR) (boxes). Values within one IQR away from the boxes are included in the whiskers, whereas more extreme values are marked as outliers (crosses).

Fig 3. Receiver operating characteristic (ROC) curves for left: optic nerve sheath diameter, (ONSD), mid: Deformability index (DI) and right: combined ONSD and DI. Area under curve (AUC) was 0.84, 0.87 and 0.98, respectively (not significantly different).

Fig 4. Measured versus estimated ICP. ICP estimated based on ONSD (left), DI (mid) and combined ONSD and DI (right). Regression formula for estimation of ICP was $ICP = 4.8 \cdot ONSD\text{-}5.8$ ($R^2 = 0.18$), $ICP = 30 - 43 \cdot DI$ ($R^2 = 0.52$), and $ICP = 4 + 4.3 \cdot ONSD\text{-}42 \cdot DI$ (R^2=0.67), respectively.

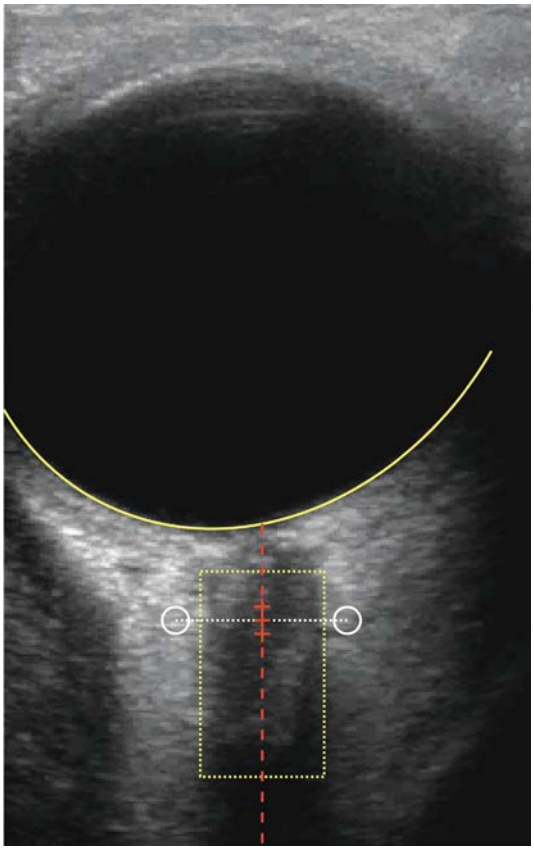

Fig 1

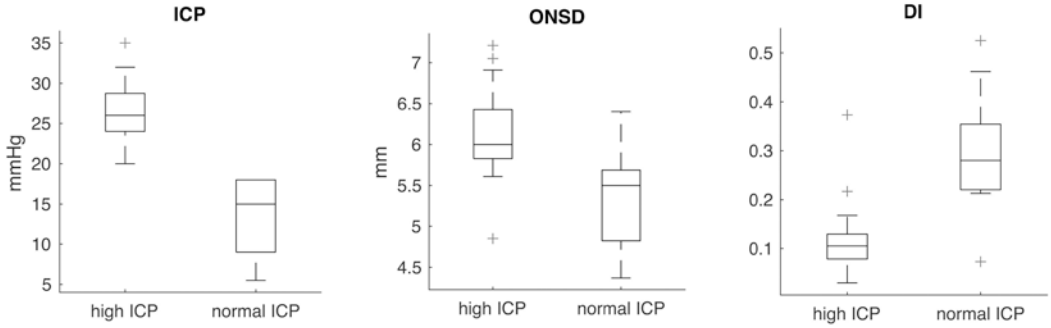

Fig 2

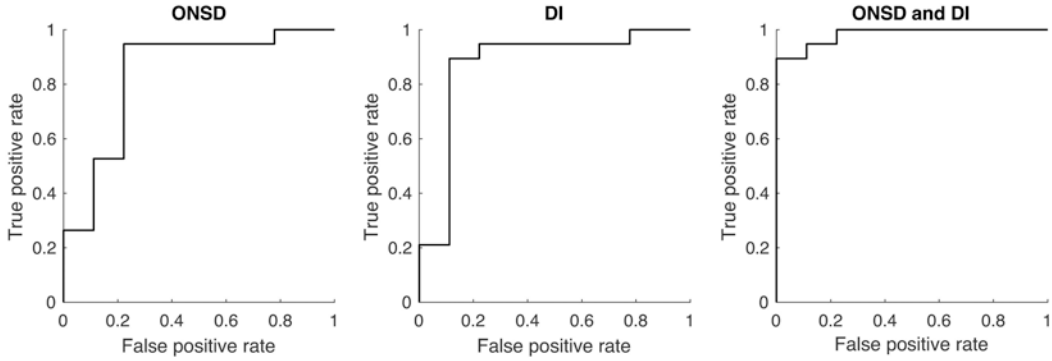

Fig 3

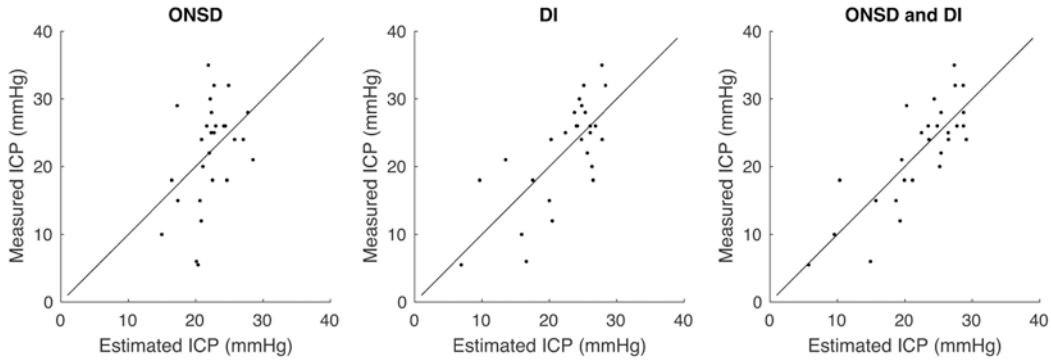

Fig 4