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Optic nerve sonographic examination to predict raised intracranial pressure in idiopathic intracranial hypertension: The cut-off points

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Abstract

Purpose: Monitoring of raised intracranial pressure (ICP) in patients with idiopathic intracranial hypertension (IIH) is required to prevent secondary optic nerve damage. Sonographic measurement of the optic nerve sheath diameter (ONSD) is a noninvasive method to evaluate intracranial hypertension. Different ONSD cut-off values have been reported probably due to ethnic variations. Our aim was to determine optic nerve sonographic examination cut-off points to predict raised ICP in IIH patients.

Methods: This case-control study was conducted on 99 IIH post-pubertal female patients (both probable and definite) and 35 age- and sex-matched healthy volunteers. Sonographic ONSD and optic nerve diameter (OND) were obtained 3 mm behind the posterior edge of the globe in a horizontal plane via a 7–13 MHz linear probe. Lumbar puncture was then carried out on the patients.

Results: The opening cerebrospinal fluid pressure documented in the patient group was 279.64 ± 65.97 mm H_2O. A statistically significant difference was found between IIH patients and controls regarding ONSD. The best ONSD cut-off value indicating raised ICP was 6.05 mm with an area under the curve of 0.850 (95% confidence interval 0.805 to 0.894, 73.2% sensitivity and 91.4% specificity). Regarding OND/ONSD ratio, there was an insignificant difference between both groups.

Conclusion: Sonographic ONSD but not OND/ONSD ratio could offer a bedside adjunct or alternative indicator of elevated ICP in IIH patients. Ethnic differences, however, should be noted when using this parameter.

Keywords

Optic nerve sonography, optic nerve sheath diameter, idiopathic intracranial hypertension

Introduction

Measurement of raised intracranial pressure (ICP) is a cornerstone in the diagnosis and monitoring of idiopathic intracranial hypertension (IIH).[1] This is critical because early detection and subsequent prompt treatment of cerebrospinal fluid (CSF) hypertension can prevent secondary optic nerve damage that occurs as a result of the interruption of axoplasmic transport within the pre-laminal optic nerve head, and impairment of the flow in the central retinal vein.[2,3] Currently these measurements are obtained through an invasive, complicated technique, namely lumbar puncture (LP).[4] Increased ICP is transmitted to the subarachnoid space surrounding the optic nerve, leading to optic nerve sheath expansion. It has been shown previously that the expansion of this cerebrospinal fluid (CSF) space can easily be detected using ultrasound and has a good correlation with raised ICP measured by surrogate methods.[5,6] Therefore, the aim of our study was to determine optic nerve sonographic (ONS) examination cut-off points to predict raised ICP in IIH patients.

Participants and methods

This was a case-control study including 99 post-pubertal female patients diagnosed with IIH according to the established diagnostic criteria,[1] who were compared to 35 age-matched healthy females with presumed normal ICP (based on clinical evaluation). Both definite (CSF pressure ≥ 250 mm H_2O, $n = 90$) and probable (CSF pressure < 250 mm H_2O, $n = 9$) IIH patients were

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included. Participants were excluded if they had comorbidity that may affect the visual pathway or the ICP. Patients were recruited from the Neurology Department of Kasr Al-Ainy School of Medicine, Cairo, Egypt, during a period extending from April 2012 to May 2018. Informed consent was obtained from all participants and the study protocol was approved by the local ethics committee.

Participants underwent detailed history taking, medical, neurological and ophthalmological assessment including visual acuity (by means of Snellen chart) and fundus examination. The latter and visual field testing were used to confirm and assess the grade of papilledema in the patients. Weight and height were measured to calculate body mass index (BMI) (kg/m^2). Neuroimaging, either brain computed tomography or magnetic resonance imaging, was carried out for all patients and magnetic resonance venography was performed to exclude venous sinus thrombosis. This was followed by optic nerve sonographic examination at the Cairo University Neuro-sonography Unit (CUNU), Cairo.

ONS examination

Ultrasound equipment and data acquisition. The examination was carried out using a high-resolution ultrasonography instrument (Philips IU2 xMATRIX, CA, US) with a high-resolution linear-array transducer with frequencies ranging from 7 to 13 MHz. The acoustic output of the ultrasound systems was adjusted to the requirements of ONS according to the ''as low as reasonably achievable'' principle to avoid damage to the lens and retina.[7]

The settings for sonography were as the following: for B-mode, transmit frequency was 7–13 MHz, mechanical index (MI) equal to 0.1, single focal zone at 2.5 cm and bandwidth of 74 dB.

Patient position. The participants were placed supine with heads elevated by 20–30 degrees. Their eyes were closed and they were asked to gaze forward. From above and slightly laterally, the transducer was applied with coupling of gel on the closed eyelids and with minimal pressure on the patient's orbit. By definition the nasal side was depicted on the left image side.

Measured parameters. The measurements were collected in B-mode by a certified neurosonographer. The optic nerve sheath diameter (ONSD), in 198 papilledemic eyes and 70 healthy eyes; and the optic nerve diameter (OND), in 178 papilledemic eyes and 54 healthy eyes, were taken in a position 3 mm behind the posterior edge of the globe in a horizontal plane perpendicularly to the optic nerve axis. The optic nerve was visualized as a hypoechogenic structure beyond the retina surrounded by hyperechoic subarachnoid space and hypoechoic dura mater (Figure 1). Two readings were recorded for each eye and an average measure was obtained.

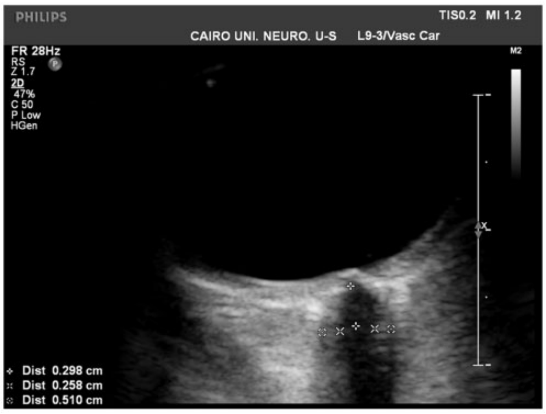

Figure 1. Sonographic measurement of the optic nerve sheath diameter, calculated by the distance between the two cursors measured 3 mm posterior to the globe.

We also calculated the OND/ONSD ratio when possible. All of the previous measurements were obtained before performing LP and starting any management.

Assessment of CSF pressure

LP was carried out as part of the patients' diagnostic workup. The opening CSF pressure was measured in the lateral decubitus position, under strict aseptic condition, without sedating the patients, by an expert neurologist. No abnormality in cell count or chemistry was detected in the CSF samples.

Statistical methods

Data were coded and entered using the statistical package SPSS version 24, IBM, USA. Data were summarized using mean, standard deviation and range for quantitative variables. Comparisons between groups were performed using the unpaired t test.[8] The compared data were normally distributed as checked by Shapiro-Wilk test and by normality plots. Receiver operator characteristic (ROC) curve was constructed with area under the curve analysis performed to detect the best cut-off value of the ONSD for detection of cases. P values less than 0.05 were considered as statistically significant. Statistical details are supplied in the Supplemental Tables 1s and 2s.

Results

Demographics and clinical data

All participants in the studied groups were post-pubertal females. IIH patients (90 definite and nine probable) had visual acuity ranging from 6/6 to 6/18 and the grade of papilledema ranged from one to four. Sixth nerve palsy was diagnosed in two patients; however, the other neurological examination results were normal. None of the controls had papilledema.

Table 1. Demographics of the participants and the clinical parameters of the patients.

	IIH group	Control group	*p* value
Age, years	31.00 ± 8.74 (16–62)	31.88 ± 9.48 (18–52)	0.677
BMI, kg/m^2	32.93 ± 7.22 (19–50)	27.49 ± 7.61 (16.7–45)	0.005[a]
Duration of illness, months	13.36 ± 10.12 (3–36)	_	_
CSF opening pressure, mm H_2O	279.64 ± 65.97	_	_

Data are presented as mean ± SD (range). BMI: body mass index; CSF: cerebrospinal fluid; IIH: idiopathic intracranial hypertension. [a]Significant.

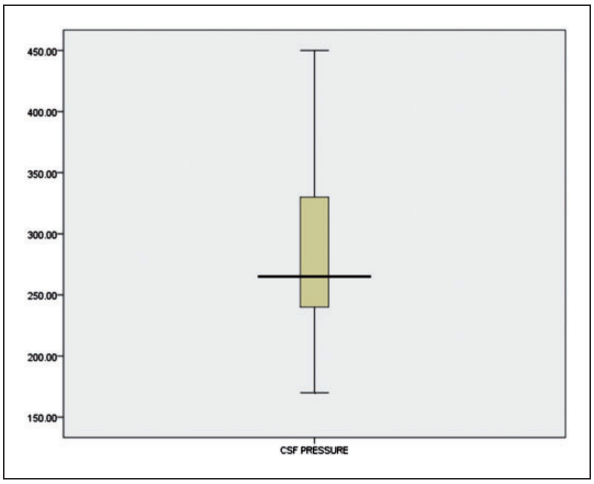

Figure 2. A box and whisker chart showing the distribution of cerebrospinal fluid (CSF) pressure measurements in idiopathic intracranial hypertension patients.

The demographics of the participants and the clinical parameters calculated for IIH patients are presented in Table 1, with significantly higher BMI in the IIH group. Figure 2 shows the distribution of CSF opening pressure measurements in IIH patients.

ONS measurements

The ONSD was measured for 99 IIH patients and 35 control individuals. OND was measured for 89 IIH patients and 27 controls. OND/ONSD ratio was then calculated when the two measurements were available. There was a statistically significant difference between the IIH group and control group regarding ONSD. It was significantly higher in the IIH group. The difference between both groups regarding OND/ONSD ratio was not statistically significant (Table 2). Moreover, we found an insignificant relation between CSF opening pressure and ONSD in linear regression (Supplemental Figures 1s and 2s).

After construction of the ROC curve of the ONSD (Figure 3), the best estimated cut-off value of the ONSD in detecting IIH was 6.05 mm. The sensitivity and the specificity were 73.2% and 91.4%, respectively (Table 3). The cut-off with 100% sensitivity was 3.1 mm and the cut-off with 100% specificity was 6.5 mm. Details of estimated cut-off values are supplied in Supplemental Table 3s.

Discussion

Invasive techniques like LP and the placement of an intracranial catheter[4,9] allow accurate measurement of raised ICP. In IIH, however, performance of LP is challenging in some situations (obesity, coagulopathy or thrombocytopenia) and has many complications such as post-spinal tap headache, local back pain, spinal subdural hematoma, infection and nerve root irritation.[4,10] Moreover, the procedure may need to be repeated when estimation of ICP can lead to modification of treatment. Relying on optic disc swelling, as an indirect method, is also not ideal since its development often occurs in late stages.[6] This emphasizes the importance of developing a simple, noninvasive tool for early diagnosis and management. Earlier reports have explored the utility of the ONSD measured by ONS in predicting or monitoring intracranial hypertension.[5,6] The ONSD is calculated 3 mm behind the globe, and perpendicularly to the vertical axis of the optic nerve as the horizontal distance between the two cursors. The measurement at that distance is not only the maximum diameter distension, but also the segment of the sheath showing the greatest ultrasound contrast.[9] Cases of asymmetrical distention of the perineural sheaths have been reported;[11] therefore, in clinical practice, the sonographic measurement of the ONSD should be performed bilaterally for confirmation purposes.[12] This is exactly what was performed in the present study. The current study on Egyptian participants showed that ONSD measurement was significantly increased in IIH patients compared to controls. Increased ONSD in our patients with elevated CSF pressure was anticipated considering that the optic dural sheath contains three portions: the intracranial, the intracanalicular and the intraorbital segments, and pressure fluctuations within the intracranial cavity easily reflected on that distensible portion surrounding the nerve.[13] A relation between CSF pressure and ONSD, however, could not be documented in the present study. Although Hansen and Helmke[14] have previously documented this relation, Ebraheim et al.,[15] similar to our result, did not find a correlation between CSF pressure measurements and ONSD. Even though the significant increase in ONSD in patients with intracranial hypertension was concordant with previous observations in neurocritical patients[5,9] as well as in studies carried out on IIH patients,[6,16,17] there is considerable variability in the cut-off points. A consensus

Table 2. Measurements of ONSD and OND/ONSD ratio in IIH patients and control individuals.

	IIH group		Control group		
	No. of examined eyes	Mean ± SD	No. of examined eyes	Mean ± SD	*p* value
ONSD, mm	198	6.57 ± 1.02	70	5.50 ± 0.40	<0.001[a]
OND/ONSD ratio	178	0.50 ± 0.15	54	0.52 ± 0.05	0.262

IIH: idiopathic intracranial hypertension; OND: optic nerve diameter; ONSD: optic nerve sheath diameter; SD: standard deviation. [a]Significant.

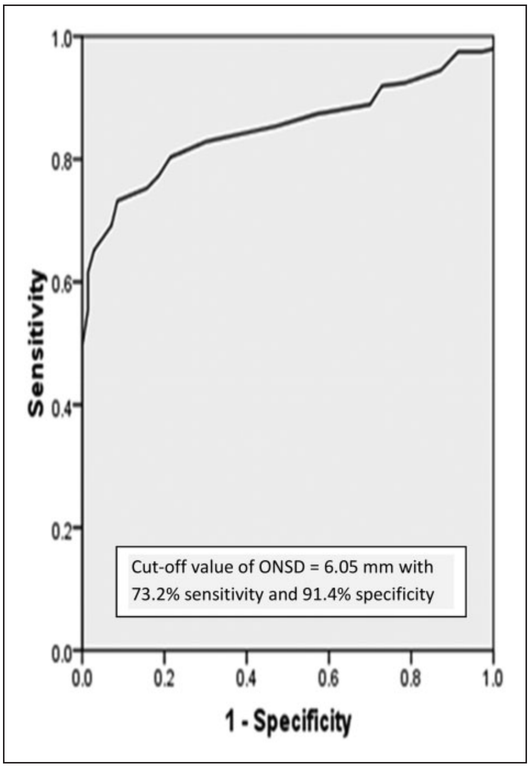

Figure 3. Receiver operator characteristic curve for optic nerve sheath diameter (ONSD) related to intracranial pressure in idiopathic intracranial hypertension. The ONSD cut-off value was 6.05 mm with an area under the curve of 0.850 (95% confidence interval 0.805 to 0.894 and $p < 0.001$).

regarding the cut-off point for an abnormal ONSD indicating raised ICP has not yet been established. Most authors have suggested that the upper normal value of ONSD is 4.5 mm for individuals 1 year old or less and 5.0 mm for those aged more than 1 year.[14,18–22] In the present study, the identified cut-off was 6.05 mm, which was notably higher than previous reports. Close figures to ours were those reported in studies conducted by del Saz-Saucedo et al.[17] in Spain (6.3 mm with 94.7% sensitivity and 90.9% specificity) and Lochner et al.[6] on German and Italian IIH patients (5.93 mm with 93% sensitivity and 67% specificity). Using different optic nerve imaging modality (computed tomography), other investigators identified a different cut-off value (5.5 mm) for the same disease.[23] Raffiz and Abdullah[9] considered ONSD measurement that exceeded 5.2 mm in a Malaysian population as abnormal. However, they defined raised ICP as being more than 20 mmHg in patients selected from a neurocritical care unit. Moreover, two European studies on brain-injured patients revealed cut-offs equal to 5.7 mm and 5.9 mm in Greece[24] and France,[5] respectively. We postulated that the differences in the findings may be a result of the rate of progression of ICP elevation, being higher in acutely ill patients. Although an accurate measurement of ICP could be achieved in neurocritical patients via the use of the gold standard, invasive intracranial catheter, alterations in ONSD may accompany critical care procedures in those patients, such as sedation or mechanical ventilation.[25] To avoid this disadvantage, the selection of IIH patients to conduct the current study was justified. Different cut-offs with different sensitivities and specificities were reported from other Asian countries. Determined cut-off points in China[26] and Iran[27] were 4.1 mm and 5.5 mm, respectively. Furthermore, Watanabe et al.[28] reported that the ONSD diameter before surgery in Japanese patients with chronic subdural fluid collection was 6.1 ± 0.7 mm and was significantly reduced after drainage operation. It is also noteworthy that the available African cut-off was 4.2 mm, as reported in a study conducted on pediatric patients in Malawi who presented with increased ICP due to acute neurological disorders.[29] The wide range in the aforementioned cut-offs and the differences between them and our results are possibly due to the variability in study designs. These include differences in the features of each study population (age, gender and neurological disorder), the lower limit identified to diagnose raised ICP, the tools used for its assessment and the imaging modalities employed to measure ONSD. To the best of our knowledge no publications regarding ultrasound ONSD measurements in IIH patients from Middle Eastern countries are available. As cut-off values vary across different races and may be influenced by genetic distinctions, our study targeted the Egyptian population to identify the cut-off value of the ONSD in IIH patients. The lack of a unified cut-off for normal and abnormal ONSD underscores the need for meta-analyses in this field. To date, there is no study that has evaluated the OND/ONSD ratio in discriminating patients with increased ICP from those without. In a Chinese study,[30] however, the estimated mean value in healthy volunteers was 0.63 ± 0.07, which was higher than our reported values in normal controls (0.52 ± 0.05) and IIH patients (0.50 ± 0.15). The authors stated that the "OND/ONSD ratio had a relatively narrow normal

Table 3. Data related to the receiver operator characteristic curve of the ONSD.

	Area under curve	Standard error	*p* value	95% Confidence interval		Cut-off value	Sensitivity %	Specificity %
				Lower bound	Upper bound			
ONSD, mm	0.850	0.023	<0.001[a]	0.805	0.894	6.05	73.2	91.4

ONSD: optic nerve sheath diameter. [a]Significant.

range and may be a promising surrogate of ONSD."[30] Our research, however, revealed that OND/ONSD ratio was insignificantly different between the patients and the controls, doubting its value in detecting raised ICP in IIH. Other secondary issues are the significantly higher BMI of IIH patients compared to healthy volunteers and the gender preference of the disease after puberty. Indeed, these findings were expected and were in accordance with previous reports. An earlier study has discussed the association between IIH, female gender and high BMI; the authors found that the incidence of IIH in young and obese women was up to 20-fold higher than in nonobese individuals.[31] In another study, the percentage of obese individuals among IIH patients reached up to 90%.[3] Furthermore, a significantly positive correlation between CSF opening pressure and BMI was documented.[6,15] The likely role of sex hormones in the pathogenesis of IIH might explain the predilection of IIH in females in the childbearing period and the rarity of the disorder in men.[31,32]

Limitations

The current study being limited to post-pubertal females did not cover the influence of factors such as gender or age category on the estimated cut-off. Moreover, assessment of OND and ONSD with ultrasound is operator dependent; therefore the availability of trained personnel is mandatory. Assessments could be unfeasible because of inadequate sonic windows or may be subject to errors of measurement related to artifact, shadowing and erroneous placement of the cursors. Furthermore, the opening pressure on LP might be altered by patient position, muscle tone, anxiety, and pressure on the abdomen.

Conclusions

Sonographic ONSD (but not OND/ONSD) might offer bedside adjunct or alternative methods to the current invasive LP in prediction of raised CSF pressure in IIH female patients. Ethnic differences, however, should be noted when using this parameter. A larger, possibly multicenter trial should be carried out to validate the results.

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Conflict of interest

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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