

Correlation of Optic Nerve Sheath Diameter and Optic Sheath to Optic Nerve Diameter Ratio with Lumbar puncture opening Pressure in Pseudotumor Cerebri Syndrome

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ABSTRACT:

BACKGROUND:

In cases of Pseudotumor Cerebri Syndrome, increased intracranial pressure is transmitted to the subarachnoid space surrounding the optic nerve, causing increase in the optic nerve sheath diameter and Optic nerve sheath to optic nerve diameter ratio. Magnetic Resonance Imaging is the image of choice in Pseudotumor Cerebri Syndrome and it can be used to measure precisely the diameter of optic nerve and its surrounding sheath.

OBJECTIVE:

To evaluate the diagnostic value of optic nerve sheath diameter, Optic nerve sheath to optic nerve diameter ratio, and their correlation with lumbar puncture opening pressure in Pseudotumor Cerebri Syndrome

PATIENTS AND METHODS:

In a prospective blinded correlational diagnostic yield study, a 3 tesla Magnetic Resonance Imaging data of 34 patients with Pseudotumor Cerebri Syndrome, and 34 normal control were collected and analyzed, optic nerve sheath diameter and optic nerve diameter were measured in an axis perpendicular to the optic nerve, 3 mm behind the globe.

RESULTS:

Both optic nerve sheath diameter and Optic nerve sheath to optic nerve diameter ratio were found to be significantly larger in patient's group compared to control. Lumbar puncture opening pressure in patient was measured and found to be correlated significantly with both optic nerve sheath diameter and optic nerve sheath to optic nerve diameter ($r = 0.79$ - $p < 0.000$, $r = 0.45$ - $p < 0.007$ respectively). The optic nerve sheath diameter in patients were 5.75 ± 0.6 mm, cut-off value for diagnoses of Pseudotumor Cerebri Syndrome was 4.9 mm with a sensitivity of 91% and specificity of 88%. The cut-off value of optic nerve sheath to optic nerve diameter ratio was 2.39 with a sensitivity of 100% and specificity of 97%.

CONCLUSION:

Magnetic Resonance Imaging -determined (optic nerve sheath diameter & optic nerve sheath to optic nerve diameter ratio) have excellent diagnostic value in Pseudotumor Cerebri Syndrome, and they were correlated significantly with LP opening pressure.

KEYWORDS: MRI, Optic nerve, Pseudotumor Cerebri Syndrome

INTRODUCTION:

Intracranial hypertension without ventriculomegaly, mass lesion, or evidence of infection characterizes the pseudotumor cerebri syndrome (PTCS).^[1] The pseudotumor cerebri syndrome may be primary [idiopathic

intracranial hypertension (IIH)] or arise from an identifiable secondary cause.^[2, 3]

The incidence of PTCS in the general population is around 1: 100,000, whereas in obese women aged 15 - 44 it is more common, at 10 - 20: 100,000.

PTCS demonstrates a strong female predominance, with a female/male ratio of 8:1.^[4, 5, 6]

Patients may present with headache, tinnitus, and diplopia most frequently from unilateral or

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OPTIC NERVE SHEATH DIAMETER LUMBAR PUNCTURE

bilateral abducens palsy, or transient visual obscurations associated with papilledema.^[7,8]

The visual manifestations of primary PTCS and secondary PTCS are similar; the earliest visual symptom is transient visual obscurations, which are episodes of visual blackout or dimming lasting seconds to minutes in one or both eyes.^[3] As the intra cranial pressure (ICP) increases, the pressure is transmitted to the optic nerve, and the optic nerve sheath acts as a tourniquet to impede axoplasmic transport.

The associated increase in cerebrospinal fluid (CSF) volume in the perioptic space results in unfolding of the optic nerve sheath and optic nerve sheath expansion, and it is believed that this, in turn, compresses the nerve, causing stasis of axonal transport, thus resulting in the characteristic swelling of the nerve head.^[9, 10, 11]

The confirmatory test in PTCS is a lumbar puncture that should follow neuroimaging to avoid a situation that might produce herniation.

Abnormal values are greater than 280 mm of CSF in children and greater than 250 mm of CSF in adults and in children of normal weight who are not sedated.^[12, 13]

Note that CSF pressure fluctuates constantly and false elevations or misleading normal values occasionally occur.^[14]

Increased ICP is transmitted to the subarachnoid space surrounding the optic nerve, causing optic nerve sheath expansion.

Measurement of the optic nerve sheath diameter (ONSD) through noninvasive imaging technologies can provide surrogate markers for early elevated ICP.^{[10][15]}

Measurement of the optic nerve sheath diameter has been studied in postmortem specimens,^[16] intrathecal infusion models^[17] children with ventriculoperitoneal shunts^[18] and emergency department patients with head injuries.^[19, 20]

Magnetic resonance imaging can be used to measure precisely the diameter of optic nerve and its surrounding sheath, by using T2-weighted sequence.^[21, 22]

Moreover, in cases of hypotension in the Cerebrospinal fluid, optic nerve sheath diameter was found to be reduced.^[23]

Optic nerve sheath to optic nerve diameter ratio (ONSD/OND) can be used as an objective method reflect raised intracranial pressure where

outer diameter of optic nerve sheath divided by optic nerve diameter at the level of maximum dilatation on coronal T2 sections.^[24]

Unfortunately there is limited reference value for ONSD. Goeres P et al. measures optic nerve sheath diameter in healthy volunteers, reporting a mean ONSD of 3.68 mm, mean ONSD did not vary with age, weight, or height but did vary with sex. Mean ONSD measurements for men were 3.78 mm compared with 3.60 mm for women.^[25]

The significance of this study is to evaluate the diagnostic value of non-invasive measures (ONSD&ONSD/OND ratio) versus invasive measures (lumbar puncture (LP) opening pressure) and to clarify their correlation in PTCS.

The aim of the study is to evaluate the diagnostic value of magnetic resonance imaging (MRI)-determined two parameters: (ONSD&ONSD/OND ratio) in PTCS and to clarify the correlation of ONSD and LP opening pressure in PTCS and the correlation of ONSD/OND ratio and LP opening pressure in PTCS.

PATIENTS AND METHODS:

This is a prospective blinded correlational diagnostic yield study performed in Al-Imamain Al-Kadhimain medical city, neurology and radiology department Patients were enrolled between September 1, 2015, and January 20, 2017.

We included a convenience sample of 34 adult patients, fulfilling the diagnostic criteria of definite PTCS^[2], and exclude pregnant ladies, patients less than 18 years of age any patient with significant history of ocular disease, ocular trauma, or ocular surgery.

34 Age matched healthy female volunteers with negative past medical and drug history and normal neurological examination recruited during the same period from the local community, underwent the same imaging protocol (apart from contrast and MRV) served as control, Pregnant ladies and those with history of ocular disease, ocular trauma, or ocular surgery had been excluded.

MRI in all individuals was performed using a 3 Tesla Magnetom Total Imaging Matrix Trio

OPTIC NERVE SHEATH DIAMETER LUMBAR PUNCTURE

(Siemens Medical Solutions, Munich, Germany). The complete routine brain MRI exam that our institution normally perform was done, (with and without gadolinium in all patients to exclude an underlying pathology other than PTCS), this included T1 axial spin echo, T2 axial turbo-spin echo, coronal Fluid-attenuated inversion recovery (FLAIR), and MRV was done finally (in patient group) to exclude venous sinus thrombosis.

The axial T2-weighted high resolution sequence was used to measure ONSD and optic nerve diameter (OND). The scan parameters were as follows: FOV 230 mm, voxel size 0.575, repetition time (TR) 3000 milliseconds, and echo time 80 milliseconds, slice thickness 4 mm.

The optic nerve sheath appeared as a high signal surrounding a region of low signal corresponding to the optic nerve. The axial image slice that provided the best view of the ONSD was chosen and assessed on the workstation, the retrobulbar area was zoomed to x300, and then ONSD and OND were measured in an axis perpendicular to the optic nerve, 3 mm behind the globe in the retroampullary region using an electronic caliper. The OND and the ONSD values obtained from both sides were averaged for comparison.

Within 24 hours after MRI, lumbar puncture was performed in the patient group in the lateral decubitus position and the opening pressure of CSF was measured, CSF sample obtained for routine analysis.

The doctor who performed the lumbar puncture was blinded to the results of ONSD and ONSD/OND ratio.

Statistical analyses

Statistical analyses were carried out using MINITAB statistical software (Version 16) and MedCalc Statistical Software (version 17.2).

Anderson-Darling Test for normality applied to age, ONSD, ONSD/OND ratio (in both patient and control) and LP opening pressures in patient, (P-value < 0.05 = not normal. Normal = P-value >= 0.05)

Two-tailed unpaired Student's t-test was used to compare ONSD and NSD/OND ratio in both patient and control.

To evaluate the diagnostic value of ONSD and ONSD/OND ratio in PTCS, receiver operating characteristic (ROC) curves were produced for ONSD and ONSD/OND ratio each separately with calculation of the best cut off value sensitivity and specificity at 95 % confidence intervals.

Using a scatter diagram The ONSD and LP opening pressure, ONSD/OND ratio and LP opening pressure distributions were tested (each separately in patient group).

The Pearson correlation coefficient r and p values for the significance of correlation were calculated for both ONSD and LP opening pressure, ONSD/OND ratio and LP opening pressure (each separately).

Values are expressed as means \pm standard deviation otherwise specified, and P values < 0.05 were considered to be statistically significant.

The value of (r) is either positive (positive correlation) or negative (inverse correlation)

$r < 0.3$ = no correlation

$r 0.3 - 0.5$ = weak correlation

$r 0.5 - 0.7$ = moderate correlation

$r > 0.7$ = strong correlation

Regression analysis with regression equation and its coefficient of determination was calculated.

RESULT:

The study included 34 patients with definite diagnoses of PTCS; all of them were females, with an average age of 32 ± 3.3 years, (range 25–37 years).

Regarding control group, 34 age-matched healthy female volunteers with an average age of 30.5 ± 2.9 years, (range 25–37 years).

The mean ONSD in the patient group was 5.75 ± 0.6 mm, ranging from 4.5 to 6.9 mm. The mean ONSD in healthy volunteers was significantly lower (4.18 ± 0.61 mm; $P = 0.000$) ranging from 3 to 5.2 mm.

The mean of ONSD/OND ratio in patient group was 2.89 ± 0.24 , ranging from 2.42 to 3.35. The mean ONSD/OND ratio in healthy volunteers was significantly lower (2.05 ± 0.22 ; $P = 0.000$) ranging from 1.56 to 2.68.

OPTIC NERVE SHEATH DIAMETER LUMBAR PUNCTURE

The mean value of LP opening pressure was 317.5 ± 47.31 mm CSF, ranging from 250 to 430 mm CSF.

To evaluate the diagnostic value of ONSD and ONSD/OND ratio in PTCS, receiver operating characteristic (ROC) curves were produced for ONSD and ONSD/OND ratio each separately, their diagnostic values classified according to area under ROC curve (AUC) (0.9-1=excellent)(0.8-0.9=good)(0.7-0.8=fair)(0.6-0.7=poor)(0.5-0.6=fail).

ONSD has excellent diagnostic value in PTCS, area under ROC curve (AUC) = 0.965 (95%

confidence interval = 0.889 to 0.994; $P = 0.0001$). Figure 1

The best cut-off value of ONSD was 4.9 mm, with a sensitivity of 91%, a specificity of 88% and a negative predictive value of 90% and a positive predictive value of 88%.

One hundred per cent sensitivity and negative predictive values were achieved for a 4.45 mm ONSD cut-off but with a specificity of 64%.

One hundred per cent specificity and positive predictive values were achieved for a 5.2 mm ONSD cut-off but with a sensitivity of 76%.

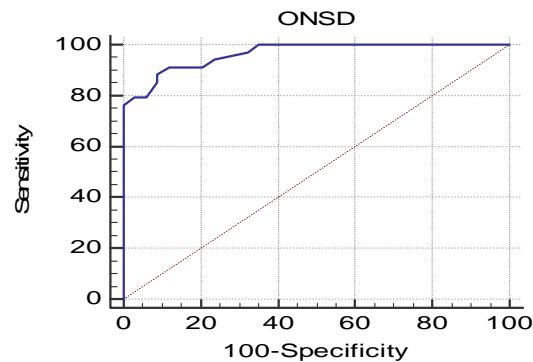


Figure 1: ROC curve for ONSD as a diagnostic test in PTCS, with the best cut-off value of 4.9 mm (sensitivity of 91%, specificity of 88%)

ONSD/OND ratio has excellent diagnostic value in PTCS, area under ROC curve (AUC)= 0.992(95% confidence interval = 0.933 to 1.000; $P = 0.0001$) Figure 2.

The best cut-off value of ONSD/OND ratio was 2.39, with a sensitivity of 100%, a specificity of

97% and a negative predictive value of 100% and a positive predictive value of 97%.

One hundred per cent specificity and positive predictive values were achieved for a 2.68 cut-off but with a sensitivity of 73%.

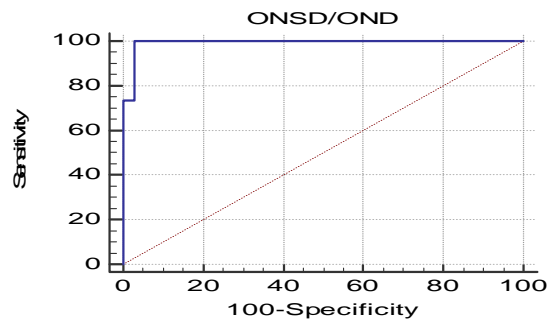


Figure 2: ROC curve for ONSD/OND ratio as a diagnostic test in PTCS, with the best cut-off value of 2.39(sensitivity of 100%, specificity of 97%)

OPTIC NERVE SHEATH DIAMETER LUMBAR PUNCTURE

The relationship between ONSD and LP opening pressure was illustrated by scattergram of LP opening pressure as a function of ONSD. (Figure 3)

Furthermore, using the Anderson-Darling Test for normality, the ONSD values had a p-value of 0.25 and LP opening pressure values had

a p-value of 0.09, both were consistent with a normal distribution, thus the pearson correlation coefficient was used to assess the relationship. A significant and strong positive linear relationship was found between ONSD and LP opening pressure ($r = 0.79$ $p=0.000$).

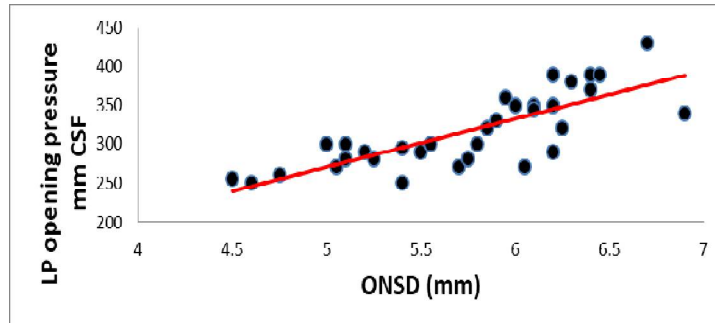


Figure3: Scatter gram of LP opening pressure versus ONSD, identified a strong and significant positive relationship.

The relationship between ONSD/OND ratio and LP opening pressure was illustrated by scattergram of LP opening pressure as a function of ONSD/OND ratio. (Figure 4)

Furthermore, using the Anderson-Darling Test for normality, the ONSD/OND ratio values had a p-value of 0.06 and LP opening pressure

values had a p-value of 0.09, both were consistent with a normal distribution, thus the pearson correlation coefficient was used to assess the relationship. A weak but significant positive relationship was found between ONSD/OND ratio and LP opening pressure ($r = 0.45$ $p= 0.007$).

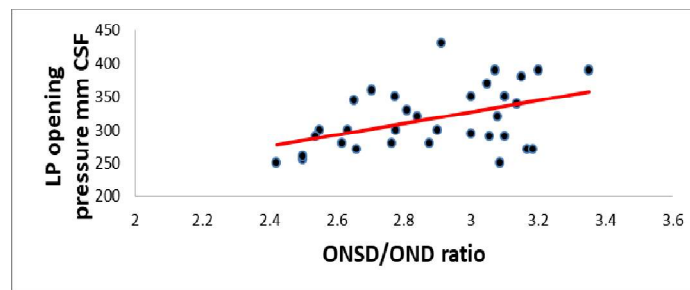


Figure 4: Scatter gram of LP opening pressure versus ONSD/OND ratio, identified a weak but significant positive relationship.

OPTIC NERVE SHEATH DIAMETER LUMBAR PUNCTURE

Simple linear regression analysis was used to predict lumbar puncture opening pressure depending on ONSD. The regression equation is:

Lumbar puncture opening pressure = - 39.2 + 61.9 ONSD.

The coefficient of determination is 62.7%.

DISCUSSION:

This study sought to correlate noninvasive MRI measurements of ONSD and ONSD/OND ratio with invasive measurement of ICP using LP opening pressure in PTCS. Our findings confirm that LP opening pressure in patient was correlated significantly with both ONSD and ONSD/OND ratio (r 0.79- p 0.000, r 0.45- p 0.007 respectively).

To the best of our knowledge this is the first study to date, that clarify the correlation of both ONSD and ONSD/OND ratio with LP opening pressure in PTCS.

The mean age of the patients in our study was 32 years; this is expected as the disease is more common in young adult, its prevalence increase between 15-44 years of age.^[5, 6]

All patients in our study were female (we did not exclude male) although PTCS has strong female predominance with a female/male ratio of 8:1, but our sample has a stronger female predominance, may be due to small sample size.^[4, 5, 6]

The mean of ONSD in PTCS group was significantly higher than normal volunteers group (5.75 mm and 4.18 mm respectively).

This confirms the previous studies findings of increase ONSD in PTCS.^[26, 27, 28, 29]

The mean of ONSD/OND ratio in PTCS group was significantly higher than normal volunteers group (2.89 and 2.05 respectively).

These readings go with Lingawi study, which showed that patients with idiopathic intracranial hypertension had ONSD/OND ratios higher than normal volunteers.^[30]

Regarding LP opening pressure we include patients with definite diagnoses of PTCS only, who had pressure more than 250 mm CSF.

According to the results of ROC curves, both ONSD and ONSD/OND ratio showed excellent diagnostic value for PTCS (AUC was 0.965, 0.992 respectively).

In our study we detected a lower cut off value for ONSD of 4.9 mm (with a sensitivity of 91% and a specificity of 88%) than previous studies, in Bekerman et al. who evaluated CT scan data of 35 adult patients with PTCS, the cut-off value of ONSD was >5.5 mm, however Bekerman et al. did not measure sensitivity and specificity.

Degnan et al. MRI based retrospective study described a cut-off value of ONSD of 5.8 mm in PTCS with sensitivities of 86.9% and specificities of 76.1%, in both Bekerman et al. and Degnan et al. the cut-off value of ONSD was for both male and female, while in our study all patients were female, which can explain the difference in cut-off value and in sensitivity and specificity.^[26, 27]

However one hundred per cent sensitivity and negative predictive values were achieved for a 4.45 mm ONSD cut-off but with a specificity of 64%, and one hundred per cent specificity and positive predictive values were achieved for a 5.2 mm ONSD cut-off but with a sensitivity of 76%.

In the light of this result, ONSD < 4.45 mm is helpful in exclusion of PTCS, while ONSD > 5.2 mm is helpful to confirm the diagnoses of PTCS. The best cut-off value of ONSD/OND ratio was 2.39, with a sensitivity of 100%, a specificity of 97%.

However one hundred per cent specificity and positive predictive values were achieved for a 2.68 cut-off but with a sensitivity of 73%.

In the light of this result, ONSD/OND ratio < 2.39 mm is helpful in exclusion of PTCS, while ONSD/OND ratio > 2.68 mm is helpful to confirm the diagnoses of PTCS.

This goes with Lingawi study, which showed that a ratio ≥ 2.5 is highly suggestive of the diagnosis of IIH.^[30]

Both ONSD and ONSD/OND ratio showed significant positive linear correlation with LP opening pressure, the correlation was strong with ONSD and weak with ONSD/OND ratio, this allowed the use of ONSD as a predictive value for LP opening pressure, however the coefficient of determination is 62.7 %, in other word 62.7 % of LP opening pressure can be predicted accurately using this regression model.

Several studies have demonstrated that the enlargement of the ONSD is strongly correlated with increased ICP in emergency department and neurocritical care patients.^[15, 31, 32]

Hansen et al. have showed that the ONSD increases linearly in most persons with the increase in ICP after a pressure threshold is achieved; this threshold ranging between 20.4-40.8 cmH₂O and the expansion has been shown to be reversible.^[17]

Lingawi study showed that ONSD/OND ratio and LP opening pressure was correlated but did not measure the correlation coefficient of this correlation.^[30]

In conclusions MRI-determined (ONSD&ONSD/OND ratio) have excellent diagnostic value in PTCS. ONSD has strong positive significant linear relationship with LP opening pressure in PTCS. ONSD/ONS ratio has weak positive but significant linear relationship with LP opening pressure in PTCS.

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