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ORIGINAL ARTICLE

Diagnostic performance of ocular ultrasonography compared to fundoscopy to predict papilledema

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ABSTRACT

BACKGROUND: The aim of this study was to determine the association between the diameters of optic nerve sheath assessed by ultrasonography, grading of papilledema in fundoscopy among patients suspected to raising intracranial pressure and determining the sensitivity and specificity of ultrasonography to detect optic nerve sheath dilatation.

METHODS: This prospective blinded cohort study was performed on 223 consecutive patients with clinical suspicion to optic papilledema. The patients were assessed using direct fundoscopy. The diameter of the optic nerve sheath was determined by ocular ultrasonography.

RESULTS: In fundoscopy, 46 patients were revealed to have papilledema in at least one of the two eyes. A significant correlation was found between diameter of optic nerve sheath and age in total population as well as in those without papilledema, but not in the group with papilledema. The mean diameter of optic nerve sheath in bilateral assessment was significantly higher in the group with papilledema. The association between the mean diameter of optic nerve sheath and grade of papilledema was strongly significant. The assessment of the area under ROC analysis showed that measuring diameter of optic nerve sheath could effectively discriminate papilledema from normal condition.

CONCLUSIONS: Ultrasonography can effectively discriminate papilledema from normal condition by measuring diameter of optic nerve sheath.

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Key words: Ultrasonography - Papilledema - Intracranial hypertension - Optic nerve.

Papilledema is mainly characterized by optic disc swelling secondary to elevated intracranial pressure due to a wide spectrum of cerebral pathological conditions such as intracranial tumor lesions, venous sinus thrombosis, inflammation, and ventricular obstruction or encephalitis.[1] The pathophysiological basis of this phenomenon is based on axoplasmic flow stasis accompanied with intra-axonal edema.[2] Following an increase in intracranial pressure, this pressure may transfer to the optic nerve sheath leading to swelling of the nerve head and thus active nerve inactivation. Despite its rare occurrence, it may appear at any age with no sex and racial predilection.[3] Clinically, manifestations of papilledema are mostly secondary to increased intracranial pressure including headache, nausea and vomiting, pulsatile tinnitus, impaired vision, diplopia, and visual acuity impairment in very advanced

stages of disease.[4] To the best working-up of the disease, neuroimaging is the first consideration for discovering any causes of elevated intracranial pressure.[5] The most common imaging modalities employed to assess the origins of the disease include CT scan and magnetic resonance imaging (to identify mass lesions), venography (to detect venous thrombosis of the sinuses), optical coherence tomography (to assess elevating the nerve fiber layer), fluorescein angiography (to diagnose capillaries dilatation), and ultrasonography (to detect buried disc drusen).[5-7]

According to the pointed subjects, dilatation of the optic nerve sheath is an earlier manifestation of raising intracranial pressure. This change in optic nerve sheath can be easily visualized via ultrasonography, as a noninvasive and available imaging modality.[8] Using this method, detecting dilation of the optic nerve sheath 3 mm behind the eye is possible. In other words, by developing high frequency linear ultrasonic probes, viewing the optic nerve sheath and its abnormal change following papilledema has been enabled.[9, 10] However, the diagnostic accuracy of this method compared to fundoscopy as the gold standard for detection and grading papilledema remains uncertain. Furthermore, the optimal optic nerve sheath diameter cut-off for the identification of intracranial hypertension has not been established. The present study primarily aimed to determine the association between the diameter of optic nerve sheath assessed by ultrasonography and grading of papilledema in fundoscopy among patients with suspected raising intracranial pressure. Then, the sensitivity and specificity of ultrasonography to detect optic nerve sheath dilatation was determined with introducing the best cutoff value of optic nerve sheath diameter to discriminate optic papilledema from normal condition.

Materials and methods

Study population

This prospective blinded cohort study was performed in Emergency of Army hospital on 223 consecutive patients with clinical suspicion of optic papilledema. The inclusion criteria were severe headache (score higher than 7 out of 10 based on the visual analogue scaling method), decreased level of consciousness within the last 24 hours, severe vomiting more than three times, occurrence of seizure during the last 12 hours, and the appearance of focal neurologic deficits during the last 24 hours. Those with the following criteria were also excluded from the study: age less than 18 years, hemodynamic instability, impossibility of conducting optic ultrasonography because of anatomic abnormalities, skin, dissatisfaction or lack of cooperation, and impossibility of performing fundoscopy because of the anatomic abnormalities or lack of cooperation. The study protocol was explained to patients and their relatives and informed consent was obtained before participation in the study.

This study was approved by the ethics committee of Qazvin University of Medical Science. Informed consent was obtained from parents. Human rights were respected in accordance with the Helsinki Declaration. After explaining a detailed description of the study to parents or legal guardians of infants, the written consent was taken from them.

Study protocol

First, baseline characteristics including demographics, patients' complaints, the history of raised intracranial pressure, and receiving any medication were recorded. Second, to detect the evidences of papilledema, the patients were assessed using direct fundoscopy in sitting or lying position by a single resident of emergency medicine. If necessary and in absence of contraindications, the pupils were dilated by dropping tropicamide. Then, in supine position and after rubbing the ultrasound gel on the closed eyelids, the eyes were examined by ocular ultrasonography using superficial probe by an emergency medicine specialist remained unaware of the results of fundoscopy and the diameter of the optic nerve sheath was determined 3 mm behind the eye, three times measurements for each eye. Finally, the mean

of six times of measurements for each patient was considered as the mean overall diameter of optic nerve sheath.

Study endpoints

The primary study endpoint was to determine the diagnostic value of ultrasonography to detect optic nerve sheath dilatation compared to optic fundoscopy. The second end point was to determine the best cutoff value of optic nerve sheath diameter, to predict optic papilledema.

Statistical analysis

For statistical analysis, results were presented as mean±standard deviation (SD) for quantitative variables and were summarized by absolute frequencies and percentages for categorical variables. Normality of data was analyzed using the Kolmogorov-Smirnoff Test. Categorical variables were compared using χ^2 test or Fisher's Exact Test when more than 20% of cells with expected count of less than 5 were observed. Quantitative variables were also compared with *t*-test or Mann-Whitney U Test. The association between the diameter of optic nerve sheath and grading of papilledema was assessed using the Pearson's Correlation Test. The ROC curve analysis was used to determine the value of cystatin C to discriminate acute kidney injury from a normal condition. Also the best cutoff value of optic nerve sheath diameter yielding the most appropriate sensitivity and specificity was also determined. For the statistical analysis, the statistical software SPSS version 16.0 for windows (SPSS Inc., Chicago, IL, USA) was used. P values of 0.05 or less were considered statistically significant.

Results

Of 223 patients initially eligible for the study, only 222 were finally assessed (the excluded subjects were 8 because of inability to perform fundoscopy, 5 who were younger than 18 years, 4 because of satisfaction in participation in the study and 4 because of hemodynamic instability). The mean age of participants was 43.93±20.00 years (with the median of 42 years) that 49.1% of them were female. Severe vomiting was the most common complaint reported in 23.9%, followed by severe headache in 22.5%, decreased level of consciousness in 19.8%, focal neurologic deficits in 17.1% and seizure in 16.7%. The mean systolic and diastolic blood pressures were 136.71±20.05 mmHg, and 89.32±13.35 mmHg, respectively. The fundoscopy was performed in lying position for 105 patients, and in sitting position for 117 patients. In fundoscopy assessment, 46 patients revealed to have papilledema, at least in one eye (two patients suffered unilateral lesion because of the unilateral intra-cerebral hemorrhage). Table I compares the baseline characteristics between the groups with and without papilledema. The patients with papilledema were significantly older than those without this lesion, however, no difference was revealed in the sex distribution between the two groups. None of the patients in two groups had a history of raised intracranial pressure. Using the correlation coefficient test, a significant correlation was found between the diameter of optic nerve sheath and age in total population (rho =0.576, P<0.001) as well as in those without papilledema (rho =0.533, P<0.001), but not in the group with papilledema (rho =0.137, P=364). In the patients' group, the mean diameter of optic nerve sheath on the right-sided was 4.78±0.83 mm and on the left-sided was 4.77±0.86 mm with no difference (P=0.642). The mean diameter of optic nerve sheath in bilateral assessment was significantly higher in the group with papilledema when compared to those without papilledema (6.16±0.32 mm

TABLE I.—*Baseline characteristics and clinical data in patients with and without papilledema.*

Item	Group with papilledema	Group without papilledema	P value
Mean age, year	56.91±16.36	40.54±19.51	<0.001
Female gender, %	21 (45.65)	88 (50.00)	0.665
Education level, %			0.442
Undergraduate	13 (28.26)	55 (31.25)	
Diploma-bachelor	29 (63.04)	103 (58.52)	
Master or higher	4 (8.70)	18 (10.22)	
Marriage, %	29 (63.04)	79 (44.89)	0.056

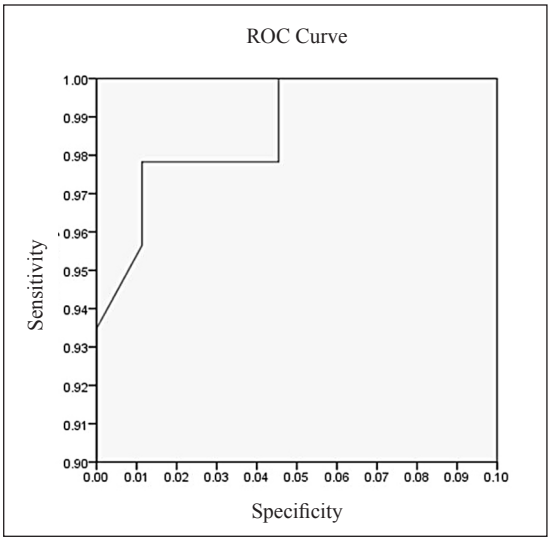

Figure 1.—Area under the ROC cure analysis to determine value of diameter of optic nerve sheath to discriminate papilledema from normal condition.

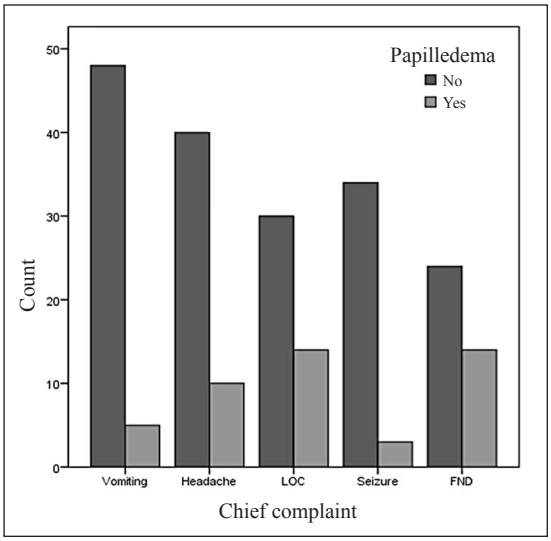

Figure 2.—The presence of papilledema according to the patients' chief complaints.

versus 4.42±0.46 mm, P<0.001). In total, the association between the mean diameter of optic nerve sheath and grade of papilledema was strongly significant (rho =0.700, P<0.001). The assessment of the area under the ROC analysis (Figure 1) showed that measuring diameter of optic nerve sheath could effectively discriminate papilledema from a normal condition (AUC =0.998, P<0.001). The best cutoff value of diameter of optic nerve sheath assessed by ultrasonography to predict papilledema was shown to be 5.62 mm yielding a sensitivity of 97.8%, a specificity of 98.9%, a positive predictive value of 95.7%, a negative predictive value of 99.4%, a positive likelihood ratio of 88.90, and a negative likelihood ratio of 0.02.

As shown in Table II, a comparison of the blood pressures between the two groups with and without papilledema showed higher systolic, diastolic and mean blood pressures in the former group. For all study subjects, a significant association was revealed between diameter of optic nerve sheath and systolic blood pressure (rho =0.577, P<0.001), diastolic blood pressure (rho =0.461, P<0.001) and mean blood pressure (rho =0.478, P<0.001). The association between diameter of optic nerve sheath and systolic, diastolic and mean blood pressures remained significant in those without papilledema (rho =0.657, 0.502, and 0.676 respectively, P<0.001), however, this association was insignificant in those with papilledema (rho =0.010, 0.157, and 0.132 respectively, P>0.05 for all). The prevalence of papilledema was the highest in the patients with focal neurologic deficits (36.8%) followed by those with loss of consciousness (31.8%), headache (20.0%), vomiting (9.4%), and seizure (8.1%) (Figure 2).

TABLE II.—*Systolic, diastolic and mean blood pressure in patients with and without papilledema.*

Item	Group with papilledema	Group without papilledema	P value
Systolic BP, mmHg	144.78±19.40	136.60±19.73	<0.001
Diastolic BP, mmHg	93.48 ±10.79	88.24±13.76	<0.001
Mean BP, mmHg	110.58±12.01	103.69±14.38	0.012

Discussion

For several years, determining diameter of optic nerve sheath has been identified as a reliable marker for assessment of intracranial hypertension because of its strong correlation with raised intracranial pressure and papillede-

ma. Also, the application of ultrasonography for detection of optic disc swelling has been recently studied. However, the best threshold of the diameter of optic nerve sheath — measured by ultrasonography to differentiate papilledema caused by increased intracranial pressure from normal status — has remained unclear. The present study could first show that the assessment of the diameter of optic nerve sheath by ultrasonography could effectively predict optic nerve sheath abnormality due to intracranial hypertension with high sensitivity and specificity. In fact, by using ultrasonography, the need for using fundoscopy to assess the presence of papilledema can be eliminated. In this regard, we also obtained a cutoff value of 5.62 mm for optic nerve sheath diameter to detect papilledema and its high grades. The high diagnostic performance of ultrasonography to predict intracranial hypertension has been shown in several studies. As indicated by Shirodkar *et al.* in 2014,[11] sensitivity of detecting raised intracranial pressure by optic nerve sheath diameter was 84.6% in females and 75% in males while specificity was 100% in both genders. In another study by Wang *et al.* in 2015,[12] the optic nerve sheath diameter cut-off point for the identification of elevated intracranial pressure was 4.1 mm and yielded a sensitivity of 95% and a specificity of 92%. As shown by Golshani *et al.*,[13] the calculated sensitivity and specificity of ophthalmoscopy and ultrasonography in detection of intracranial pressure rising were 100.0% and 35.4%, 100.0% and 31.9%, respectively which was considerably lower than those obtained in our survey. Kimberly *et al.*[14] also revealed that optic nerve sheath diameter of more than 5 mm performed well to detect raised intracranial pressure with a sensitivity of 88% and specificity of 93% and that the cutoff value and diagnostic performance were near to our obtained values. Similarly to our survey, Frumin *et al.*[15] could obtain that optic nerve sheath diameter of more than 5.2 mm of detected raised intracranial pressure with a sensitivity of 83.3% and specificity of 100%. Almost all studies could demonstrate the high value of measuring optic nerve sheath diameter with a cutoff value ranging from 5.0 to 5.2 mm to predict raised intracranial pressure, which was also confirmed in our study. According to the positive association between intracranial pressure and its adverse consequences such as papilledema, ultrasonography can be introduced as an accurate noninvasive procedure to detect papilledema due to raising intracranial pressure. As shown also by Mehrpour *et al.*,[16] considering 5.7 mm as the upper limit for normal optic nerve sheath diameter, sensitivity and negative predictive value of optic ultrasonography in diagnosis of pseudopapilledema are 100% for both eyes. In total, because of the impossibility of fundoscopy for detection of papilledema and its grading and also some limitations of this method, the use of ultrasonography seems to be superior for the detection of papilledema.[17-20]

Conclusions

Ultrasonography can effectively discriminate papilledema from normal condition by measuring the diameter of the optic nerve sheath.

References

1. Scott CJ, Kardon RH, Lee AG, Frisén L, Wall M. Diagnosis and grading of papilledema in patients with raised intracranial pressure using optical coherence tomography vs clinical expert assessment using a clinical staging scale. Arch Ophthalmol 2010;128:705-11.
2. Vaphiades MS. The disk edema dilemma. SurvOphthalmol 2002;47:183-8.
3. Friedman DI. Papilledema and idiopathic intracranial hypertension. Continuum (Minneap Minn) 2014;20(4 Neuro-ophthalmology):857-76.
4. Rajajee V, Vanaman M, Fletcher JJ, Jacobs TL. Optic nerve ultrasound for the detection of raised intracranial pressure. Neurocrit Care 2011;15:506-15.
5. Shirodkar CG, Munta K, Rao SM, Mahesh MU. Correlation of measurement of optic nerve sheath diameter using ultrasound with magnetic resonance imaging. Indian J Crit Care Med 2015;19:466-70.
6. Bäuerle J, Schuchardt F, Schroeder L, Egger K, Weigel M, Harloff A. Reproducibility and accuracy of optic nerve sheath diameter assessment using ultrasound compared to magnetic resonance imaging. BMC Neurol 2013;13:187.
7. Kulkarni KM, Pasol J, Rosa PR, Lam BL. Differentiating mild papilledema and buried optic nerve head drusen using spectral domain optical coherence tomography. Ophthalmology 2014;121:959-63.
8. Neudorfer M, Ben-Haim MS, Leibovitch I, Kesler A. The efficacy of optic nerve ultrasonography for differentiating papilloedema from pseudopapilloedema in eyes with swollen optic discs. Acta Ophthalmo 2013;91:376-80.

9. Hoffmann J, Huppertz HJ, Schmidt C, Kunte H, Harms L, Klingebiel R, *et al.* Morphometric and volumetric MRI changes in idiopathic intracranial hypertension. Cephalalgia 2013;33:1075-84.
10. Carter SB, Pistilli M, Livingston KG, Gold DR, Volpe NJ, Shindler KS, *et al*. The role of orbital ultrasonography in distinguishing papilledema from pseudopapilledema. Eye (Lond) 2014;28:1425-30.
11. Shirodkar CG, Rao SM, Mutkule DP, Harde YR, Venkategowda PM, Mahesh MU. Optic nerve sheath diameter asa marker for evaluation and prognostication of intracranial pressure in Indianpatients: An observational study. Indian J Crit Care Med 2014;18:728-34.
12. Wang L, Feng L, Yao Y, Wang Y, Chen Y, Feng J, *et al*. Optimal optic nerve sheath diameter threshold for the identification of elevated opening pressure on lumbarpuncture in a Chinese population. PLoS One 2015;10: e0117939.
13. Golshani K, Ebrahim Zadeh M, Farajzadegan Z, Khorvash F. Diagnostic Accuracy of Optic Nerve Ultrasonography and Ophthalmoscopy in Prediction of ElevatedIntracranial Pressure. Emerg (Tehran) 2015;3:54-8.
14. Kimberly HH, Shah S, Marill K, Noble V. Correlation of optic nerve sheath diameter with direct measurement of intracranial pressure. Indian J Crit Care Med 2015;19:466-70.
15. Frumin E, Schlang J, Wiechmann W, Hata S, Rosen S, Anderson C, *et al*. Prospective analysis of single operator sonographic optic nerve sheath diameter measurement for diagnosisof elevated intracranial pressure. West J Emerg Med 2014;15:217-20.
16. Stone MB. Ultrasound diagnosis of papilledema and increased intracranial pressure in pseudotumor cerebri. Am J Emerg Med 2009;27:376.e1-376.e2.
17. Shofty B, Ben-Sira L, Consantini S, Freedman S, Kesler A. Optic nerve sheath diameter on MR imaging: establishment of norms and comparison of pediatric patients with idiopathic intracranial hypertension with healthy controls. AJNR Am J Neuroradiol 2012;33:366-9.
18. Mehrpour M, OliaeeTorshizi F, Esmaeeli S, Taghipour S, Abdollahi S. Optic nerve sonography in the diagnostic evaluation of pseudopapilledema and raised intracranial pressure: a cross-sectional study. Neurol Res Int 2015;2015:146059.
19. Chiang J, Wong E, Whatham A, Hennessy M, Kalloniatis M, Zangerl B. The usefulness of multimodal imaging for differentiating pseudopapilloedema and true swelling of the optic nerve head: a review and case series. Clin Exp Optom 2015;98:12-24.
20. Xu W, Gerety P, Aleman T, Swanson J, Taylor J. Noninvasive methods of detecting increased intracranial pressure. Childs Nerv Syst 2016;32:1371-86.

Conflicts of interest.—The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

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