A Case-control Study of Widened Interpalpebral Fissures in Hypertension of Idiopathic Intracranial

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Abstract

To investigate if a relationship exists between idiopathic intracranial hypertension and widened interpalpebral fissures. This is a retrospective case-control study comparing eyelid measurements, including margin-reflex distance and palpebral fissure distance, in diagnosed patients with hypertension of idiopathic intracranial according to International Classification of Headache Disorders (ICDH) 3-beta criteria and in age-matched controls. Patients with hypertension of idiopathic intracranial were 42 and 120 controls were included. All patients were Middle-East Caucasians and the mean age in the disease group was 34 ± 7 years and in the control group 35 ± 6 years (p=0.28). The disease group had 81% female patients compared to 60% female patients in control group (p=0.01). For group of disease, mean margin-reflex distance (5.36 ± 0.31 mm) and mean palpebral fissure distance (10.84 ± 0.75 mm) values were significantly higher compared to the corresponding values in control group (4.01 ± 0.26 mm and 9.39 ± 0.62 mm, respectively) (p<0.01 for both comparisons). Patients suffering from idiopathic intracranial hypertension may have widened palpebral fissures with increased margin-reflex and palpebral fissure distances. These easily recognizable signs may assist in the early management and diagnosis of this debilitating disease.

Key Words: Debilitating Disease, Hypertension, Idiopathic Intracranial.

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Introduction

Hypertension of Idiopathic intracranial (IIH) is a case where intracranial pressure elevated (ICP) with no identifiable reason [1]. The diagnosis of IIH is based on clinical suspicion and exclusion of other conditions.

Although headache is a well-known presenting character of IIH, it's usually non-specific and may not always be helpful in reaching a diagnosis. Idiopathic intracranial hypertension may also be asymptomatic, with the main clue for the condition being the incidental discovery of optic disc swelling. The diagnosis is usually confirmed by documenting increased ICP and excluding organic causes for the headache or the papilledema.

Since manifestations of IIH may be nonspecific, the correct diagnosis may be delayed until significant damage to the visual function has already occurred. It is therefore important to explore other diagnostic tools that may hold clinical value in early detection of the disease.

We have noticed from our clinical experience that some patients who were eventually diagnosed with IIH had previously presented to us at the ophthalmology clinic with headache or non-specific symptoms and apparently widened interpalpebral fissures (IPF) or lid retraction for which no explanations were found at that time. The study objective is to investigate if a association exists among IIH and widened interpalpebral fissures. We compare related measurements to the globe position and eyelids among patients diagnosed with IIH and age- and sex-matched controls.

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Methodology

This is a retrospective case-control study with participants recruited from the neurology center at Al-Diwaniyah University Hospital, Diwaniyah, Iraq between February 1st, 2013 and December 30th, 2018. The study group consisted of consecutive patients who were diagnosed with IIH by an expert headache specialist neurologist with fulfillment of the International Classification of Headache Disorders (ICDH) 3-beta headache criteria due to IIH [2]. Consecutive age-matched controls were selected from patients who were diagnosed in the same time period with tension-type headache by the same specialist neurologist until the number of individuals in this group reached 120. Willing participants from both groups were recruited for examination at the ophthalmology clinic by a consultant ophthalmologist at two separate visits.

The protocol study was verified via the Institutional Review Board at University of Al-Diwaniyah, Diwaniyah, Iraq, and a consent written format was obtained from all patients and healthy individuals.

For all participants, existing medical records were reviewed, and no patients' identifiers were kept in record. A complete ophthalmological history was obtained and in addition to a standard ophthalmological examination, measurements for globe and eyelid positions were documented as follows:

A standard metric digital Vernier caliper (nearest to 0.01 mm) was used to measure the Margin Reflex Distance (MRD) as the patient in resting position and gaze of primary. MRD definition is distance between the margin of upper eyelid and light reflex central corneal, whereas Palpebral Fissure Distance (PFD), defined as distance between the lower and upper margins of eyelid in cornea vertical axis. Due to potential effect of the level of activity in the sympathetic nervous system and the possible variability in these values, the participants were asked to come in on two separate occasions, about two weeks apart, and were advised to have a good night sleep, not to engage in strenuous physical activity, and not consume certain medications or excessive amounts of coffee or alcohol before presenting. For each of these parameters, the final value used in statistical analysis represented the mean of the readings taken from both eyes and from the two separate visits. Individuals with differences in measurements in either parameter between the two eyes or the two visits of more than 1 mm were excluded. Participants with ptosis, defined as the upper eyelid being < 2 mm from the central corneal light reflex and/or if asymmetry of two mm or moreis there between upper eyelids levels, were also excluded. Because enophthalmos or exophthalmos may affect the position of the eyelids, the level of globe protrusion was also measured using a standard Hertel exophthalmometer. Participants with values <14 or >21 mm or with a difference of >2 mm between 2 sides were excluded from both groups.

Exclusion criteria also included incomplete medical records and conditions that may result in exophthalmos or affect eyelid position including history of orbital disease, eyelid or facial trauma, thyroid disease, Cushing disease or syndrome, myasthenia gravis, familial periodic paralysis, midbrain disease, focal brain disease, hydrocephalus, head and neck surgery or trauma, high myopia, buphthalmos, and the use of medications including sympathomimetic drugs and injections of botulinum toxin within 3 months of the measurements.

Collected data were applied through Excel 2007 to an electronic database where analyses were carried out statistically by version 16.2.4 Minitab (Minitab Inc., State College, PA, USA). Unpaired Student t test was used to compare continuous data from different groups and the paired test for data within the same group. Test of Fisher's exact was applied for analysis variables of categorical. Significant value is considered when value of *p* less than 0.05.

Results

Two patients were excluded from the group of IIH due to incomplete medical record and high myopia (-10 D) and 5 patients from the control group due to incomplete medical record, history of thyroid disease, high myopia (-15 D), and history of neck surgery, 42 IIH patients and 120 controls were recorded.

Ethnicity and age were well-matched between the two groups, whereas for gender, 81% of patients at study group in comparison to 60% in the standard group were female (p=0.01). Both patients groups were Middle East Caucasians (Table 1). For the participants, the mean differences for in the values of globe protrusion, MRD, and PFD between the right and left sides were within the set values of the inclusion criteria and were not statistically significant (p>0.22 for all in-group comparisons).

When comparing the IIH and control groups, the mean globe protrusion was similar whereas both the mean MRD and PFD values were of significant

differences higher in group of IIH (figure 1). Furthermore, Table 2 shows the mean differences in mean MRD and PFD values between the right and left sides which were significantly less in group of IIH in comparison to the standard group.

Table 1. Patient's demographic features with hypertension of idiopathic intracranial and in standard

	Number	Age in years (mean ± SD [range])	Female gender (number [%])
IIH	42	34 ± 7 [18-45]	34 [81%]
Control	120	35 ± 6 [18-45]	72 [60%]
P value		0.28	0.01

Table 2. Patient's eyelid and eyeball measurements with hypertension of idiopathic intracranial and in standard

	Globe protrusion*	Margin- reflex distance (MRD)*	Palpebral fissure distance (PFD)*	Variability of MRD between right and left sides*	Variability of PFD between right and left sides*
IIH	16.8 ± 1.7	5.36 ± 0.31	10.84 ± 0.75	0.22 ± 0.20	0.22 ± 0.11
Control	17.1 ± 1.8	4.01 ± 0.26	9.39 ± 0.62	0.30 ± 0.24	0.34 ± 0.20
p value	0.34	<0.01	<0.01	0.04	<0.01

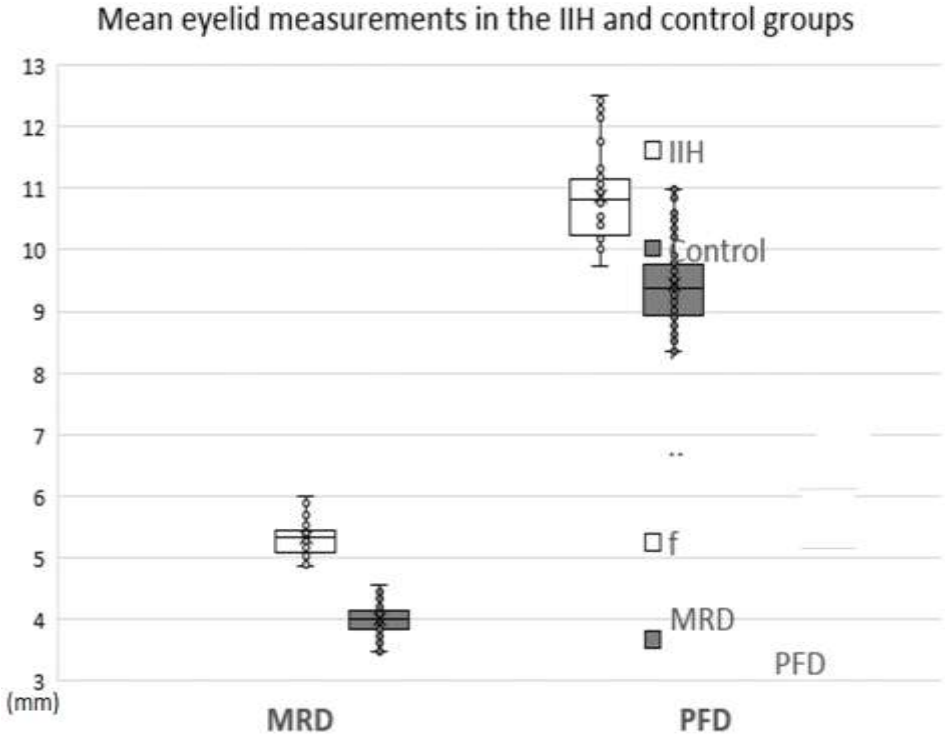

Figure 1. Box and whisker chart depicting the mean values of margin-reflex distance and palpebral fissure distance in patients with hypertension of idiopathic intracranial and in standard

Discussion

Hypertension of Idiopathic intracranial (IIH) is a puzzling condition with serious morbidity. For population in general, its overall incidence is about 2 per 100,000 with predominance of female and is more common in obese individuals [3]. With its association with obesity and globally considering the epidemic obesity, the IIH incidence is rising and the affected age groups are becoming younger [4].

With disabling chronic headaches and the risk of visual loss, IIH is not considered a benign condition [5]. It is estimated that initially rise to 22% for patient cases that have few impairment degree of visual acuity and more than 90% have abnormal perimetry function [6] [7]. Eventually, permanent vision loss can occur in up to 25% of patients [7].

Clinical diagnosis might not easily establish early at disease course. Although headache is the commonest presenting symptom, it may not be reliable enough to establish a diagnosis. Headache associated with IIH is usually non-specific and can be non-persistent, which makes it difficult to differentiate from the more common types of headache [8]. Indeed, up to 5% of general population may routinely suffer from what's known as a daily chronic headache (CDH) [9]. The International Headache Society have concluded in

their (ICDH) publication that CDH is mainly attributed to tension chronic and headache migraine, and that headache associated along IIH may actually simulate either one. Furthermore, CDH and IIH may confusingly coexist in the same patient [2,10]. Other symptoms for patients with IIH include transient visual obscurations, pulsatile tinnitus, dizziness and diplopia [11]. These complaints, however, may not be classically disclosed by the patient unless specifically inquired about.

When examining a patient with IIH, papilledema is an essential sign. However, it may not appear until late in the disease, may be asymmetric or unilateral, or may be absent altogether [12-14].

Therefore, the recognition of novel clinical features at the level of history taking and physical examination can be advantageous in the early diagnosis and avoidance of complications in IIH. In this retrospective case-control study, we have found values of MRD and PFD were of significant greater for patients of IIH in comparison to standard. The mean MRD and PFD values of 5.36 mm and 10.84 mm, respectively, in our IIH cohort, were 1.35 mm and 1.45 mm, respectively, more than corresponding values in the control cohort. In addition, the variability in MRD and PFD values between the right and left sides was of significant lower for patients of IIH in comparison to standard. This confirms our clinical observation that some patients diagnosed by neurology with IIH may have presented to the ophthalmology clinic with widened palpebral fissures at an earlier time in the course of their disease. With collaboration between ophthalmology and neurology, this clinical presentation pattern, being relatively easy to measure without allocation of much time and resources, may help in the early recognition and management of IIH.

In the literature, neuroimaging findings associated with IIH have been reported for both signs in the eyeball i.e. globe aspect of posterior flattening, sheath of optic nerve distension and optic nerve tortuosity, and signs in the brain such as slit-like ventricles and empty sella turcica. Apart from flattening posterior globe, most of these radiological signs may not be helpful for reaching a diagnosis in the clinical setting [15]. As to best for our current knowledge, the current study is the 1st one that recognize a relationship between idiopathic intracranial hypertension and clinical signs in the eyelids, including widened palpebral fissure and elevated upper lid.

There was no disparity in the distribution of ethnicity among our study (IIH) and control groups as all participants in our report were Middle East Caucasians. Age was also well-matched among the groups whereas a significant predominance of female was nticed. It's been shown that there may be significant variability in eyelid measurements among normal populations based on ethnicity but not gender [16]. Therefore, baseline characteristics in our groups should not confound our results. Furthermore, the female preponderance in our IIH group is consistent with known epidemiology of IIH in which up to 90% of individuals affected are females with age of childbearing [17].

Our finding of bilateral elevated upper lids in patients with IIH may be explained by a central mechanism where there is increased stimulation of both levator palpabrae superioris muscles. Anatomically, both levator palpabrae muscles are innervated by a single central caudal division of the oculomotor nucleus [18]. The premotor excitatory network controlling the central caudal nucleus is thought to originate from the rostral mesencephalon while the inhibitory inputs originate in the nuclear complex of the posterior commissure nucleus. It's been reported that lesions in the area of the posterior commissure may result in bilateral upper eyelid retraction [19]. With the posterior commissure nucleus closely located dorsal to the upper end of cerebral aqueduct, it is possible that elevated intracranial pressure may affect the function of the posterior commissure nucleus, which may result in lid retraction.

Study limitations are the retrospective design along bias risks of inherent, the variability in time since diagnosis of IIH by the neurology department and patients' recruitment for eye examination, and the fact that some of the patients had previous treatment or were on active treatment for IIH at time of recruitment, which may have affected any clinical feature that the condition may have produced. Various strength points in our investigation which includes its design which includes a large control group encompassing triple the number of cases of IIH in order to improve statistical accuracy. Furthermore, age and ethnicity were well-matched among the groups and strict exclusion criteria were applied to conditions or behaviors that may affect eyelid and eyeball measurements. Finally, to avoid person-to-person variability, the diagnosis of IIH in all cases was made according to ICDH criteria by one specialist neurologist and the eyeball and eyelid

measurements in all recruited cases were taken by one specialist ophthalmologist.

Conclusion

Hypertension of Idiopathic intracranial is a serious condition of neurological that may result in significant visual deficit. According to its symptoms of non-specific, clinical diagnosis of IIH might delayed. Widened palpebral fissures with increased margin-reflex distance and palpebral fissure distance values may be novel clinical signs of the disease. Recognition and measurement of these signs is safe and easy and may be helpful in the early diagnosis of IIH.

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