

Intracranial pressure in patients with papilloedema

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ABSTRACT

Objectives

Papilloedema is a clinical manifestation of chronically raised ICP, often seen in idiopathic intracranial hypertension (IIH). However, the extent of intracranial hypertension required to produce papilloedema is not known. We compare ICP values in IIH patients who developed papilloedema and those who did not. We aim identify a pathological ICP threshold predictive of the development of papilloedema in IIH patients.

Materials and Methods

Single centre cohort of IIH patients (2006 – 2016) who underwent 24-hour ICP monitoring (ICPM) and ophthalmology assessments, prior to intervention. Papilloedema was graded according to the Frisén scale. An unpaired t-test compared 24-hour ICPM between papilloedema and no-papilloedema groups. Fisher's exact test was used to determine predictive value of ICP.

Results

Thirty-six patients with IIH (35 F: 1M), mean age 32.5 ± 9.49 years (mean \pm SD). Patients with papilloedema had a mean median 24-hour ICP of 10.4 ± 5.32 mmHg (n=25), significantly higher than the group without papilloedema 6.31 ± 3.30 mmHg (n=11) ($p < 0.05$). The papilloedema group were exposed to higher pressures (10mmHg) for 30 minutes or more. Using 24-hour median ICP of 10 mmHg as a minimum cut-off predictive value gives a specificity=91%, sensitivity=48%, PPV=92% and NPV=44% of detecting papilloedema.

Conclusions

A 24-hour ICP of 10 mmHg or more is a good predictor for papilloedema and reflects a pathological threshold. The range varied widely suggesting papilloedema can occur at even lower pressures. These results are consistent with emerging evidence suggest that pathologically 'high' 24 hrs ICP is lower than previously quoted.

Key Words

Cerebrospinal fluid (CSF), headache, hydrocephalus, neuroophthalmology, vision and ocular movements

INTRODUCTION

There remains some uncertainty as to the definitive thresholds of raised intracranial pressure (ICP). Much of our current understanding of ICP levels has its foundations in monitoring following traumatic brain injury, which has led to 20 mmHg being traditionally regarded as the threshold between 'high' and 'low' ICP^{1,2-5}. There's still a considerable lack of 'Class I' evidence in this regard, and this threshold is being treated with increasing scepticism^{5, 6}.

In the context of trauma, raised ICP results from an acute loss of the compensatory reserve of the skull vault due to cerebral oedema. ICP monitoring in trauma is useful as it provides an assessment of cerebral perfusion. In contrast, chronic conditions such as idiopathic intracranial hypertension (IIH), the observed raised ICP is thought to occur due to abnormalities CSF dynamics and cerebral venous pressure⁷⁻⁹. Therefore, the application ICP thresholds used in trauma, to chronic disease process is likely to be inaccurate.

IIH (also termed pseudotumour cerebri, or benign intracranial hypertension) is a rare condition occurring in 1-3 per 100,000 patients, with preponderance for obese women of childbearing age¹⁰. IIH characterised by chronically raised ICP in the absence of any other significant pathology. IIH is diagnosed according to the modified Dandy criteria¹¹, with papilloedema the hallmark clinical sign found in nearly all patients^{11,12}. Papilloedema refers to the appearance of a swollen optic disc secondary to raised pressure in the optic nerve sheath, continuous with the CSF circulation¹². Despite supposedly being present in nearly all cases, IIH without papilloedema ('IIHWOP') has been reported, resulting in modification of the diagnostic guidelines^{11, 13-15}. There has been no study to date that has compared ICP values between IIH patients with and without papilloedema.

IIH patients with optic atrophy represent a difficult group to manage. At this centre, such patients often undergo 24-hour ICP monitoring to exclude raised pressure that could result in further visual impairment. We aim to compare ICP levels in IIH patients with and without papilloedema and characterise the dangerous level of ICP in this group. By using papilloedema as a marker of chronic 'high' ICP, we also aim to identify a pathological ICP threshold predictive of the development of papilloedema.

METHODS AND METHODS

Study design

A retrospective single cohort of patients referred with suspected IIH, covering a consecutive period of 10 years, from September 2006 to September 2016. Clinical and operative records were reviewed for demographic information, duration of symptoms and interventions.

Inclusion criteria

Patients who underwent 24-hour ICPM and had bilateral papilloedema present on ophthalmology review.

Exclusion criteria

Patients with primary eye disease causing papilloedema, those without a recent ophthalmology (over 1 year), patients without 24-hour ICPM and patients who had undergone radiological or surgical intervention for IIH were excluded. Patients with optic atrophy were also excluded.

Clinical examination

All patients were examined independently by an ophthalmologist. Retinal photography was used to confirm the presence of papilloedema, Snellen charts for acuity and automated kinetic perimetry (Goldmann). The Frisén method was used to categorise papilloedema: stage 0 = normal optic disc, stage 1 = very early papilloedema, stage 2 = early papilloedema, stage 3 = moderate papilloedema, stage 4 = marked papilloedema and stage 5 = severe papilloedema¹⁶.

24-hour ICPM

All patients underwent 24-hour ICPM using intraparenchymal intracranial monitoring devices (Spiegelberg GmbH & Co. KG, Hamburg). Median ICP (during day and night) was recorded. ICP data was processed using Excel (Microsoft ©, Reading). All ICPM data was analysed prospectively. ICP is presented as mmHg (1 mmHg = 1.36 cmH₂O).

Statistical tests

A paired two-tailed T-test was performed to determine if there was a significant difference in mean (of median 24-hour) ICPM between the papilloedema and non-papilloedema groups. Regression analysis was performed to determine if there was a correlation with severity of papilloedema (Frisén grading) with 24-hour ICPM. A pressure-time burden was a calculated

from the minute-by-minute ICPM data per patient. A ROC analysis (likelihood ratio) determined optimal ICPM cut-off values (exploratory value). A contingency table analysed with Fisher's exact test (with 95% confidence intervals) determine predictive value of both the optimal ICPM (reference standard) and the presence of papilloedema (index test). Those measuring the index test were not aware of the reference standard result and vice-versa. All statistical tests were performed on Prism 6.0c (GraphPad Software Inc, California).

Ethics and consent

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Ethic committee approval was not required for this type of study. All patients provided informed consent 24-hour ICPM.

RESULTS

Demographics

Thirty-six patients with IIH (35 F: 1M), mean age 32.5 ± 9.49 years (mean \pm SD) were identified. There were no significant differences in gender, age, use of acetazolamide, use of continuous positive airway pressure (CPAP) therapy for sleep apnoea (a known risk factor for papilloedema), symptom duration or time till ICPM between the papilloedema and no papilloedema group (table 1).

Clinical examination

Eleven patients had no papilloedema. Of the 25 patients with papilloedema, 6 had early disc abnormalities (Frisén grade 1-2), 12 moderate papilloedema (Frisén grade 3), 3 severe papilloedema (Frisén grades 4-5) and 4 had no grading recorded. Of the 25 patients with papilloedema, all had spared visual acuity (scoring 6/14 or more), no patients had colour vision loss and 16 patients had a peripheral field loss.

Symptomatic period

The period of time the patients reported visual symptoms did not correlate with Frisén grade ($R^2 = .02$) and had no significant deviation from zero ($p = .43$).

24-hour ICPM

Patients with papilloedema had a mean median 24-hour ICP of 10.4 ± 5.32 mmHg (range of medians 2.7 – 28.3 mmHg), significantly higher than the group without papilloedema (6.31 ± 3.30 mmHg, range of medians 1.2 – 10.8 mmHg) ($p < .025$) (figure 1). There appears to be an association with higher Frisén grade and ICP (figure 2). Regression analysis of 24-hour ICP and Frisén confirmed a positive linear correlation ($R^2 = .16$) with a significant deviation from zero ($p = .02$) (figure 2).

Pressure-time burden

Minute-by-minute data patients was analysed to determine the pressure-time burdens in the two groups (figure 3). The papilloedema group were exposed to higher pressures (10mmHg) for 30 minutes or more. The group without papilloedema were exposed to pressures between 5 mmHg to 10 mmHg for a significant period of time (over 175 minutes), but had just a few short spikes over 10 mmHg.

Predictive value of ICP in papilloedema

The optimal predictive cut-off value 24-hour ICP value was found to be 10 mmHg (likelihood ratio 5.28). Predictive values suggest pressures greater than median 24-hour ICP of 10 mmHg or more have high specificity and positive predictive value (PPV) for papilloedema (table 2, $p = .035$). The low sensitivity and negative predictive value (NPV) are consistent with the above observation that papilloedema can occur at even lower pressures.

Complications

There were no complications from performing the index test or reference standard in this group of patients.

DISCUSSION

Papilloedema is a known phenomenon in conditions with raised intracranial pressure (ICP). The mechanism is believed to relate to the transmission of raised ICP to the optic disc via the optic sheath that is continuous with the subarachnoid space. Chronic venous engorgement contributes to this high pressure. Persistent exposure to raised pressure can result in injury to

retinal ganglion cells. In this study we analyse the pressures that result in papilloedema in patients with IIH.

Patients with papilloedema have higher ICP values than patients without

We find that patients with papilloedema have higher ICP values overall than patients who did not develop papilloedema, being 10.4 mmHg vs. 6.3 mmHg respectively. We observe an additional relationship between the degree of raised ICP, and the severity of papilloedema in IIH. The Frisén papilloedema grade (FPG) showed a statistically significant correlation with ICP values that we interpret as showing a pressure-to-effect relationship; with higher ICP values more likely to lead to the development of papilloedema.

The pressure-time burden is greater in those with papilloedema

The finding that those with papilloedema have, on average, higher ICP over a period of 24-hour monitoring is not surprising. However, some patients with relatively low 24-hour ICPM exhibited papilloedema, whilst some without papilloedema had peaks of high pressure. Analysis of the minute-by-minute ICP data found that exposure to pressures over 10mmHg for 30 minutes or more was common in the papilloedema group. This suggests that exposure time (even to just relatively mild ICP) is an important factor in development of papilloedema.

Whilst the time pressure-time burden is greater in those with papilloedema, it appears that it may not affect the severity of the papilloedema. We found no relationship between duration of visual symptoms (over months) and grade of papilloedema FPG. This may reflect individual variation in compensatory mechanisms to the exposure of raised ICP.

Papilloedema in IIH

The difference between the non-papilloedema and papilloedema groups may reflect the two previously termed groups, IIH and IIH without papilloedema (IIHWOP). The term IIHWOP is becoming increasingly unpopular, with Friedman suggesting it has been inappropriately used¹⁷.

Papilloedema itself may be acute or chronic, the latter being most responsible for the development of visual field defects in patients with IIH¹⁸. While we found a wide range of symptomatic periods in patients with papilloedema, these ranged from 2 months to over 8 years and therefore are more likely to reflect chronic papilloedema.

Re-defining 'high' ICP

To date, there is no concrete evidence demonstrating 'normal' ICP. This is, in part, due to simple fact that there are not enough 'normal' patients who have undergone ICP monitoring. ICP is one of the few physiological parameters used in medicine that has one reference value for 'high' (20 mmHg), regardless of whether the pathology is acute or chronic.

Our finding that an ICP of 10mmg or more resulted in papilloedema, leads us to conclude that this pressure is pathological when chronic. This result concurs with recent evidence, in which ICP threshold values between 10 to 17 mm Hg differentiated between favourable and unfavourable outcomes patients undergoing decompressive craniectomy⁵.

The low NPV observed in our study reflects the fact that papilloedema was also observed at pressures lower than 10 mmHg. Therefore, whilst 10 mmHg may be the upper-end of pathological, for some patients it was as low as 6 mmHg. This variation may reflect individual propensity to develop papilloedema, perhaps due to anatomical susceptibility in certain patients. We stress that these values are obtained after 24-hour continuous ICPM, unlike the isolated readings obtained in head injury patients.

In 2015 Kattah and colleagues performed a similar study in patients with papilloedema using CSF pressure (CSFp) on lumbar puncture measurements¹⁹. They report CSFp of over 30 cmH₂O (22 mmHg) in patients with papilloedema, much high than our 10 mmHg (14 cmH₂O). Lumbar punctures only give a one-off measurement of ICP, and are typically performed in patients lying in a lateral position, curled up. In contrast, we measure ICP over a period of 24-hours and take into account the variety of positions a patient assumes over the course of the day. It is known that posture can have a large effect on ICP, and therefore also CSFp^{20, 21}.

Study strengths and limitations

This is a small case series given the rare nature of this condition in adults. The main strength of this study is the consistent and significant correlation of ICP with papilloedema. This research has the potential to inform clinicians which patients are most at risk of developing papilloedema, and therefore assist with prioritising treatment for vision saving interventions. Furthermore, it contributes to the ongoing debate regarding the normal thresholds of ICP.

Future research

This study has small numbers and further studies with greater numbers are needed. Further detailed analysis into intraocular changes and the pulsatility elements of measured ICP are being analysed to better understand the development of pathological processes underlying papilloedema.

Conclusion

Our results suggest that a 24-hour ICP of 10 mmHg or more is a good predictor for papilloedema and reflects a pathological threshold. Exposure time to pressures over 10 mmg is an important factor in development of papilloedema. The range varied widely suggesting papilloedema can occur at even lower pressures. These results are consistent with emerging evidence suggest that pathologically 'high' ICP is much lower than previously quoted.

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FIGURE LEGENDS

Figure 1. Median 24-hour ICPM between patients with no papilloedema (6.31 ± 3.30 mmHg) and those with papilloedema (10.4 ± 5.32 mmHg) ($p < .025$), with range presented.

Figure 2. Positive linear correlation between Frisén grade and ICP with a significant deviation from zero ($p = .02$, $R^2 = .16$)

Figure 3. Pressure-time burden (with smoothness of fit lines) calculated from minute-by-minute data for A: Papilloedema group (n=25) and B: No papilloedema group (n=11).

Table 1. Demographics

Table 2. Contingency table for papilloedema and 24-hour ICPM