Idiopathic Intracranial Hypertension:

recent concepts and developments

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Idiopathic intracranial hypertension (IIH) is a condition characterised by elevated intracranial pressure (ICP) and papilloedema, typically occurring in obese young women. The nomenclature of IIH has changed over the years, with previous terms including serous meningitis, pseudotumour cerebri and more recently, benign intracranial hypertension. The latter is now considered inappropriate for a condition in which affected individuals suffer with significant morbidity from chronic disabling headaches, together with progressive visual loss, which is severe and permanent in up to 25% of cases.[1]

Diagnosis of IIH

The diagnostic criteria for IIH were initially suggested in 1937 by Dandy and despite recent revision,[2,3] further clarification is required to highlight the universal importance of excluding venous sinus thrombosis.[4] Additionally, a cut-off for elevated CSF opening pressure needs to be specified (Table 1).

Pathogenesis of IIH

The pathogenesis of IIH remains unknown. Disordered cerebrospinal fluid (CSF) dynamics are fundamental although there is much inconclusive speculation in the literature as to whether this relates to enhanced CSF production at the choroid plexus or restricted CSF drainage at the arachnoid granulation tissue. The latter may, in turn, be compounded by increased venous sinus pressure. A wider review of this area is considered by Sinclair et al.[5]

The role of obesity in IIH

Of particular interest in IIH, is that over 93% of patients are obese.[6] In the obese population the incidence of IIH rises above 19 per 100,000, compared to 2.2 per 100,000 amongst the general population.[7,8] The prevalence of IIH is likely to rise in conjunction with the global epidemic of obesity (greater than 24% of adults in the United Kingdom are currently obese[9]) contributing to significant morbidity in young obese women over the next decade.

The association between obesity and IIH has not been satisfactorily explained and speculation regarding the role of centrally distributed adiposity and co-existing obstructive sleep apnoea remain unsubstantiated.[10,11] A number of case reports have linked IIH to Cushing's disease (a condition characterised by obesity and elevated circulating cortisol) as well as glucocorticoid therapy.[5,12,13] Although elevated serum cortisol is not observed in obesity, dysregulation of the cortisol generating enzyme, 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1) is well documented.[14] Glucocorticoids are regulated at a systemic level through the actions of the hypothalamic pituitary adrenal axis; however, at a tissue specific level, 11β-HSD1 (which converts inactive cortisone to active cortisol), fine tunes local glucocorticoid availability. 11β-HSD1 is highly expressed in adipose tissue and has a key role in regulating adipocyte differentiation.[15] Additionally, and of relevance in the female dominated condition of IIH, 11β-HSD1 exhibits sexual dimorphism (lower levels in women than men) with activity manipulated by sex hormones.

Interestingly, 11β-HSD1 has also been found to have a functional role in intraocular pressure homeostasis though the secretion of aqueous humour.[16] Aqueous humour secretion occurs via a mechanism analogous to that occurring in the embryogically-related choroid plexus which

TABLE: Diagnostic criteria for idiopathic intracranial hypertension

Symptoms, if present, of raised intracranial pressure
Signs representing elevated intracranial pressure or papilloedema
Elevated CSF opening pressure in the lateral decubitus position *(› 25 cmH2O, and only with great caution in those with a lower pressure)
Normal CSF composition
Imaging to exclude hydrocephalus, mass or structural lesion and *universal exclusion of venous sinus thrombosis (magnetic resonance or computed tomogram venography suggested)
No secondary cause of elevated intracranial pressure identified (anaemia, obstructive sleep apnoea, Guillain Barré syndrome, or drug effects e.g. antibiotics, non–steroidal anti-inflammatory drugs, vitamin A, lithium, cimetidine).

Adapted from the "Updated modified Dandy criteria (Friedman & Jacobson 2002) with suggested additions to the criteria marked with a star *.

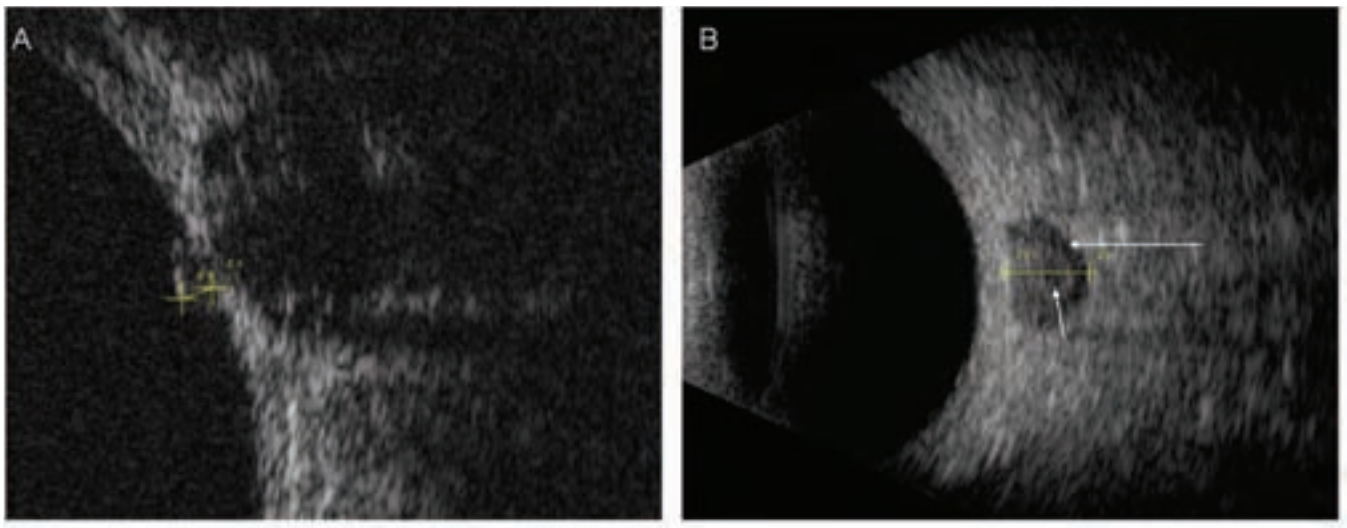
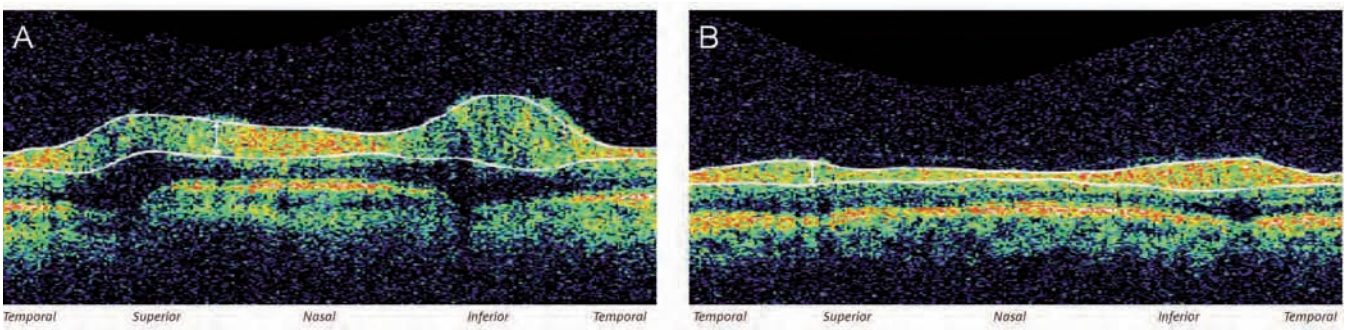


Figure 1: Ultrasonographic measurements of papilloedema. (A) Sagittal section through the orbit with the callipers measuring the maximal optic disc height (20Hz B-scan), (B) illustrates a cross section through the optic nerve sheath, the callipers mark the maximal inter-pial diameter (10Hz B-scan). The long arrow marks the hypodense signal from the cerebrospinal fluid within the distended optic nerve sheath and the short arrow marks the optic nerve.



Optical coherence tomography scan illustrating a cross sectional image acquired from scanning around the circumference of the optic disc. The arrows mark the retinal nerve fibre layer (RNFL). (A) Illustrates distension of RNFL in a patient with papilloedema, (B) illustrates the same patient following resolution of the papilloedema with a corresponding decrease in the height of the RNFL. A reduced RNFL should be interpreted in the context of the optic disc appearance and visual field assessment, as a decrease in the RNFL could also indicate progression to optic atrophy.

secretes CSF. It is possible that akin to the regulation of intraocular pressure, 11β-HSD1 may also have a role in the regulation of CSF secretion at the choroid plexus. This is endorsed by the finding of 11β-HSD1 activity, as well as expression of key element of the glucocorticoid signalling cascade, in the rabbit and human choroid plexus.[17,18] Within the eye, glucocorticoids are also known to elevate intraocular pressure through actions at the trabecular meshwork (the primary drainage tissue in the eye), as noted in topical dexamethasone induced glaucoma. Arachnoid granulation tissue has a similar structure to ocular trabecular meshwork and although little is known regarding the precise mechanisms which control drainage of CSF, glucocorticoids may also be important in manipulating CSF drainage.[18] Amongst individuals with IIH, global 11β-HSD1 activity has been noted to decrease in conjunction with weight loss, improvement in symptoms and falling ICP. Furthermore, in these patients, the reduction in 11β-HSD1 activity significantly correlated with falling ICP.[24] Glucocorticoids and 11β-HSD1 may, therefore, be important in ICP dynamics and obesity in IIH and their role, along with the therapeutic potential of 11β-HSD1 inhibitors, is currently being explored.

Treatment in IIH

The 2005 Cochrane review highlighted that an evidence base for the treatment of IIH has never been established.[19] Medical therapies (such as acetazolamide and diuretics) are widely utilised, with surgical intervention (typically CSF shunting or optic nerve sheath fenestration) typically reserved for those with rapidly deteriorating vision.

The most recent and largest randomised controlled study to assess treatment in IIH evaluated the efficacy of acetazolamide and failed to demonstrate a beneficial effect.[6] Although the study was under-powered (n=50) it highlighted that acetazolamide was extremely poorly tolerated, with 48% of subjects discontinuing acetazolamide (all at doses of less than 1500 mg per day) through choice or due to side effects, typically nausea and parasthesia.[20] The current extensive use of acetazolamide in IIH needs to be questioned in light of these results and further studies are awaited to clarify the situation. The Neuro-Ophthalmology Research Disease Investigator Consortium (NORDIC group) began enrolment to a multi-centre US trial in January 2010, aiming to recruit 154 patients in a randomised, placebo controlled trial of acetazolamide (www.ClinicalTrials.gov identifier: NCT01003639); hopefully this study will shed further light on the area. The therapeutic value of topiramate has also been considered in IIH: an open-labelled pilot study (n=40) demonstrated a beneficial effect on the visual field grade (of a comparable magnitude to that observed in a concurrently treated cohort taking acetazolamide).[21] However, interpretation of this result is significantly limited as the study was not placebo controlled or masked.

One of the most frequently advocated treatments for IIH is weight loss, although until recently evidence for the efficacy of this approach has been limited to a prospective study, carried out over 35 years ago, which noted subjective improvement in the papilloedema in nine subjects with IIH on a low calorie rice diet.[22] This report has now been superseded by a study in which individuals with IIH (n=25) were subjected to a three month period of observation followed by a three month intensive diet, during which subjects lost a mean of 15% of body weight (around 16kg).[23] The study provides the first evidence that weight loss effectively reduces ICP (measured by lumbar puncture), as well as headaches and papilloedema, in patients with IIH. These results provide important evidence for clinicians to advise and encourage patients with IIH to embark upon and maintain a weight reducing diet in order to treat

their condition. The study was further strengthened by the use of objective outcome measures to quantify papilloedema.[23] Previously, evaluation of papilloedema has relied upon subjective assessment by the clinician, this study effectively utilised ultrasonography, to measure the optic disc height and optic nerve sheath diameter (Figure 1), as well as optical coherence tomography (Figure 2), to measure the peripapillary retinal nerve fibre layer (a measure of oedema and axonal detention around the optic disc).[23] Objective assessment of papilloedema in IIH marks a key advance likely to be widely adopted in clinical management as well as future research studies.

Conclusions

It is now over 100 years since IIH was first described, yet progress to determine the underlying cause, and establish an evidence base for treatment, has been remarkably slow. Obesity may have an important role in the aetiology of IIH and further studies clarifying the implications of obesity, and associated metabolic changes in glucocorticoids and 11β-HSD1, will be of interest. The potential for weight reduction to modify obesity and treat IIH, has now been confirmed. However, the difficulties for patients to achieve and maintain weight loss are universally recognised. Practical strategies to facilitate long term weight loss, within a clinical environment, now need to be considered for patients with IIH. ◆

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