The syndrome of pseudotumour cerebri and idiopathic intracranial hypertension
Clare Fraser and Gordon T. Plant

Introduction
Idiopathic intracranial hypertension (IIH) is a disorder characterized by increased intracranial pressure (ICP) of unknown cause, predominantly seen in women of childbearing age and associated with a history of recent weight gain [1]. The concept of raised intracranial pressure in the absence of a space occupying lesion was first introduced by Nonne [2] as ‘pseudotumour cerebri’ (PTC). The article in which the term was coined refers to a number of other conditions causing raised intracranial pressure in the absence of an intracranial tumour, such as communicating hydrocephalus, which would not now be classified as PTC. The term ‘benign intracranial hypertension’ became popular and was often used interchangeably with PTC. The condition was considered ‘benign’ in comparison with cases of tumour [3] but it has been argued that loss of visual function in up to 25% of cases and progression to blindness if untreated means that it should not be considered ‘benign’ as far as visual function is concerned. Hence the term IIH is now generally used.

The authors contend that PTC remains a useful term to describe patients with raised ICP who have neither hydrocephalus nor a mass lesion but in whom either a cause has been established (often a cause of intracranial venous hypertension such as dural sinus thrombosis or a dural fistula) or the patient does not have an elevated body mass index (BMI) as a potential underlying cause. There is of course a difficulty here in that the causal relationship between weight gain and the development of IIH is unknown and an increase in body mass may act synergistically with other pathogenic mechanisms such as obstructive sleep apnoea. A set of criteria, now known as the modified Dandy criteria [4], can be used to establish a diagnosis of IIH after a thorough search for an identifiable cause of PTC (see Table 1). As stated above the authors prefer to reserve the term IIH for cases associated with a high BMI but without evidence of obstructive sleep apnoea.

Recent publications have looked again at the question of weight gain in IIH, some suggesting pathogenic mechanisms which may explain how weight gain can lead to
raised ICP, others suggesting the reverse – that raised ICP is the cause of weight gain. We do, however, have further convincing evidence that weight loss results in a lowering of ICP. There are further observations regarding the possible role of narrowing of the dural sinuses, either as a primary stenosis or secondary compression.

**Diagnosis and investigations**

The diagnosis of IIH is made by the exclusion of other causative pathologies. However, there are some recent reports of features and tests that can assist in the diagnosis and monitoring of IIH.

**Ophthalmic features**

A cross-sectional analysis and comparison of the features of IIH patients with and without papilloedema has been carried out. Among 353 patients studied, the prevalence of those without papilloedema was 5.7% (n = 20). Patients without papilloedema reported photopsias (20%) and were found to have spontaneous venous pulsation (75%) and nonphysiologic visual field constriction (20%) more often than did those with papilloedema. Mean opening pressure, although above normal, was lower in patients without papilloedema (309 versus 373 cmH₂O), but visual acuities were similar between groups [5]. A case report of a patient with IIH and monocular papilloedema documents progressive optic atrophy and central field loss in the eye without papilloedema. Despite this, the authors caution against attributing vision loss to raised ICP when there is no papilloedema [6]. Another case this year emphasizes that optic nerve sheath fenestration may yield initial improvement in vision and reduction in papilloedema yet not prevent subsequent visual loss in IIH despite the improvement in the optic disc appearance and resolution of transient visual obscurations. If there is further visual loss, a cerebrospinal fluid (CSF) diversion procedure should be considered if ICP is high [7].

When there are visual field changes in IIH without papilloedema, nonphysiological visual loss may be the underlying problem. In one review of functional visual loss (FVL) and IIH, 65% of patients had FVL at presentation and all had tubular or nonphysiological constriction of visual fields. The majority had significant psychiatric, psychosocial, or other medical comorbidities. Of concern is that 53% were managed surgically at some point, having nerve decompression, shunt, or both [8].

**Disc imaging and visual field analysis**

Optical coherence tomography (OCT) gives clinicians the ability to quantify the thickness of the retinal nerve fibre layer (RNFL) at the optic disc. The data from a recent study support the possible use of OCT as a noninvasive quantitative method of monitoring the severity and evolution of papilloedema in IIH. In a cohort of patients with mild papilloedema associated with IIH, the RNFL thickness was 75% (78.5 micron) greater than

**Table 1 Modified Dandy criteria**

<table>
<thead>
<tr>
<th>Symptoms of raised intracranial pressure</th>
<th>Headache, nausea, vomiting, transient visual obscurations or papilloedema&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>No localizing signs</td>
<td>With the exception of abducens (CN VI) palsy&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>The patient is awake and alert</td>
<td>With no evidence of cerebral thrombosis</td>
</tr>
<tr>
<td>Normal CT and MRI findings&lt;sup&gt;c&lt;/sup&gt;</td>
<td>With normal CSF biochemical and cytological composition</td>
</tr>
<tr>
<td>Lumbar puncture opening pressure &gt;25 cmH₂O</td>
<td></td>
</tr>
<tr>
<td>No other explanation for raised intracranial pressure&lt;sup&gt;d&lt;/sup&gt;</td>
<td></td>
</tr>
</tbody>
</table>

Data from [4].

<sup>a</sup>It is now well established that IIH can occur without headache and indeed without papilloedema.

<sup>b</sup>Although others can occur rarely such as conjugate gaze palsies and facial palsy.

<sup>c</sup>In most cases the imaging is not normal but shows changes secondary to raised intracranial pressure such as intra-sellar arachnoid herniation, distension of the optic nerve sheaths and flattening of the posterior aspect of the globe. These changes are not specific to IIH.

<sup>d</sup>Syndromically, in adults, most IIH patients are females with a high body mass index and a history of recent weight gain. The authors recommend putting cases who do not have this phenotype in a different category (for example a slim male). These patients can be said to have the ‘pseudotumour cerebri syndrome’ but not IIH as the diagnosis must remain under permanent review in such patients.
in control eyes and correlated significantly with Humphrey visual field indices of mean deviation and pattern standard deviation. Regression analysis showed that for every 10 micron of mean RNFL thickness increase at baseline, there was a 0.6-dB decrease in mean deviation at the last follow-up [9]. However, in more severe examples of papilloedema becoming atrophic it would be expected that thinning of the nerve fibre layer would be associated with visual loss.

**Dural venous sinus stenosis and compression**

A ‘self-sustained venous collapse’ is proposed as a crucial causative mechanism in predisposed patients, leading to intracranial hypertension in the presence of a wide range of triggering factors. The proposed mechanisms predict the long-term remission of IIH syndromes frequently observed after a single or few serial CSF subtractions by lumbar puncture [10]. Controversy remains as to whether venous sinus stenosis is consequent upon or is causative of the raised ICP.

**Imaging**

Sinus venous stenoses have been found at magnetic resonance venography (MRV) in the large majority of IIH patients in one study [10]. However, a Spanish group reports that only 58% of PTC patients showed filling defects in the transverse sinus [11]. These stenoses may have various conformations, ranging from functional smooth narrowing of sinus segments associated or not with definite flow gaps, to segmental hypoplasia or aplasia of one or more central venous collectors.

Anatomical variations must be considered when interpreting these images. Computed tomographic venography demonstrates both the morphology of the venous system and the adjacent bony grooves so provides an insight into the cause of observed narrowings of the transverse sinuses. A study from King’s College Hospital in 2008 was able to demonstrate a strong correlation of bony groove height with venous sinus height at the largest portions of the transverse sinus in both IIH patients and non-IIH individuals. They concluded that transverse sinus tapered narrowing in individuals without IIH and in the majority of patients with IIH were associated with proportionately small or absent grooves, and these were postulated to be primary or fixed. Some patients with IIH demonstrated tapered transverse sinus stenoses with disproportionately large bony grooves, suggesting a secondary or acquired narrowing [12]. This observation has important implications as it indicates that we need to consider three possible reasons why a dural sinus such as the lateral sinus may appear narrow in a patient with PTC: it may be congenitally narrow, it may be compressed secondarily to the ICP itself, or it may be an acquired stenosis.

In addition there are structures that may result in MRI venographic filling defects, such as trabeculae/septa and arachnoid granulations, all of which could ultimately lead to increased intracranial dural sinus venous hypertension. However, in normal individuals, over 50% were found to have structures in their transverse sinuses that could be potential venous filling defects [13].

**Intervention**

With the recent emphasis on the significant number of patients with IIH found to have associated nonthrombotic dural venous sinus stenosis there has been renewed interest in endovascular stenting as a treatment option. However, the assumption that venous stenosis leads to a high-pressure gradient that decreases CSF resorption through arachnoid villi requires further evidence.

In one case report, authors describe a patient with IIH who was found at venography to have a giant arachnoid granulation in the left dominant transverse sinus and in whom venous sinus stenting reduced the cerebral spinal fluid opening pressure with immediate symptomatic improvement, suggesting a causal relationship between venous outflow obstruction and IIH [14]. Another Australian report describes a woman with IIH in whom a repeatedly demonstrated venous obstruction on MRV partially resolved when the CSF pressure was reduced to 11 cmH₂O and completely resolved when reduced to 8 cmH₂O. These findings support the view that raised pressure is the cause rather than the outcome of venous obstruction [15].

In a more recent publication, 13 patients with refractory IIH were evaluated for venous sinus stent placement. Moderate sinus stenoses with normal intra-sinus pressures were found in three patients and therefore stent placement was not performed. Ten patients had elevated pressure gradient across a stenosis (11–50 mmHg), which decreased following unilateral transverse sinus stent placement. Headaches improved or resolved in all stented patients. Papilloedema resolved completely or almost completely in eight patients and significantly improved in two patients. There were no major periprocedural complications [16].

A review of published cases to date found 78% had complete relief or improvement of their main presenting symptoms after endovascular stenting. Resolution or improvement in papilloedema was seen in 85.1% of patients. The study concluded by saying that endovascular stenting should be considered whenever venous sinus stenosis is diagnosed in patients with IIH [17].

**Other pathophysiological advances**

Other disorders of venous circulation, such as jugular valve insufficiency, have also been investigated in recent
years, based on reflux duration during a controlled valsalva manoeuvre. Jugular valve insufficiency was found to be significantly more frequent in patients with IIH (70% as opposed to 30% in a control group) and may facilitate pressure transmission from increased intra-abdominal pressure in obesity into the intracranial venous system [18].

Waist-to-hip ratio (WHR) is a descriptive measure of body fat distribution approximately reflecting upper to lower body fat ratio. In a study of IIH patients compared with two obese control groups, WHR was 0.79 in IIH versus 0.84 and 0.91 in the controls. The authors concluded that in IIH, fat tends to preferentially accumulate in the lower body relative to other obese women of the same BMI range. Whereas most complications of obesity, such as hypertension, diabetes, dyslipidaemia, and the metabolic syndrome, are linked to upper body adiposity, IIH may represent a unique condition potentially induced by nonvisceral fat-related mechanisms [19].

Contrary to the obesity hypothesis, one group reported findings of similar BMI in chronic tension type headache patients and IIH patients, who did differ significantly in lumbar CSF pressure (20 as opposed to 35 cmH$_2$O). They concluded that this refutes the hypothesis that obesity precedes, and is the cause of, intracranial hypertension in IIH. Since a relationship between raised ICP and obesity is established it is therefore necessary to propose that intracranial hypertension is the primary cause of weight increase in IIH [20]. Also, in the Asian population only 7.1% of IIH patients classify as obese according to BMI, suggesting that obesity may not play a major role in the pathogenesis of IIH in Asians [21].

Recent studies have linked obesity with abnormalities in circulating inflammatory and adiposity-related cytokines [22]. Obesity is also related to dysregulation of cortisol production by the prereceptor enzyme, 11beta-hydroxysteroid dehydrogenase, and this may have a role in pathogenesis [23]. In a study of 26 patients, CSF leptin was significantly higher in patients with IIH compared to controls. In the control population, BMI correlated with serum and CSF leptin, but this was not the case for the IIH population. This suggests that CSF leptin may be important in the pathogenesis of IIH and that obesity in IIH may occur as a result of hypothalamic leptin resistance [24]. However, another study found there was no alteration in leptin levels but did show an elevation in CSF cytokine CCL2 [25]. Yet another study found that no significant differences in the serum and CSF concentrations of cytokines IL-1beta, tumour necrosis factor (TNF) and IP-1 were observed between the IIH and controls, suggesting these cytokines do not contribute to pathogenesis [25]. Both natriuretic peptides and aquaporin-4 were proposed as potential factors in vascular dysregulation affecting the CSF; however, studies recently published have failed to find an association with IIH [26,27].

A recent study has looked again at the question of thrombophilia in IIH. In a cohort of 51 patients with obesity-related IIH, the presence of antiphospholipid antibodies was significantly associated, as were elevated levels of factor VIII, plasminogen activator inhibitor-1 and lipoprotein(a). How these results should be interpreted is difficult to say as any evidence of thrombosis per se is outwith the clinical definition of IIH [28].

**Management**

Dural venous sinus stenting has shifted management focus in some institutions, but this should be considered on balance with other options for normalizing ICP.

**Lifestyle**

It has long been taught that acetazolamide is used to protect patients from the potential harm of IIH while they are losing enough weight to reverse the pathological process, with little top-level evidence. However, results from the first formal study of lifestyle intervention were published this year. In this study, 25 women with a BMI above 25, who had papilloedema and intracranial pressure greater than 25 cmH$_2$O for over 3 months, underwent a dietary modification. The protocol followed three stages, each of 3 months duration:

1. Stage 1: no new intervention  
2. Stage 2: nutritionally complete low calorie diet (425 kcal/day)  
3. Stage 3: follow-up period after the diet.

All measures of weight, IIH symptoms and visual function remained stable over stage 1. During stage 2, there were significant reductions in weight (mean 15.7 kg), ICP (mean 8.0 cmH$_2$O), score on headache impact test (7.6), and papilloedema. Mean deviation of the Humphrey visual field remained stable, and in five patients the Log MAR visual acuity improved by one line. Fewer women reported symptoms including tinnitus, diplopia, and obscurations. Re-evaluation at 3 months after the diet showed no significant change in weight, and all outcome measures were maintained. This study shows for the first time that women who followed a low-energy diet for 3 months had significantly reduced signs and symptoms of IIH and that these reductions persisted for three months after they stopped the diet [29].

**Medical**

Reducing the production rate of CSF can be achieved using acetazolamide (a carbonic anhydrase inhibitor), and this still the mainstay of medical therapy. Frusemide, bendroflumethiazide and topiramate may also be used, in
those intolerant of acetazolamide. The use of corticosteroids is debatable. There have been no updates in the literature for 2009 and 2010 concerning the use of any of these medications.

A 2007 study compared topiramate versus acetazolamide in IIH, and found no statistically significant difference in outcome, except for prominent weight loss in those given topiramate [30]. A 2010 review of electronic medical records found the use of topiramate in IIH is seen particularly in patients with co-existent obesity, depression or bipolar disorder with the average dose being 100 mg per day [31].

In 2007 there was a study of the use of octreotide in the management of IIH [32]. However, there have been no subsequent publications in Medline listed journals.

**Surgical**

To date, no prospective, randomized study has been performed comparing lumbo-peritoneal shunt, ventriculo-peritoneal shunt and optic nerve sheath fenestration. Procedure choice appears to be based on local availability and the prominence of presenting symptoms. Well designed, multicentred clinical trials to clarify which intervention best suits particular patients are needed [33].

In a single-centre review of adjustable lumbo-peritoneal shunts, 77% had improvement of their headache and 86% had no ongoing visual problems postoperatively. Spontaneous readjustment of the valve occurred in one patient causing over-drainage headache, and this resolved when the valve was reset. Distal obstruction meant 35% required shunt exploration or revision procedures [34]. In another study of four patients treated with lumbo-peritoneal flow-regulated shunts, the device was found to be a satisfactory treatment for those who require surgical therapy [35]. Further experience is required to address the long-term outcome of adjustable shunts, balancing sufficient drainage while preventing over-drainage [36].

A review of the literature examining the use of bariatric surgery in IIH was published, reporting on a total of 62 patients. The Roux-en-Y gastric bypass was the most common bariatric procedure performed. Over 90% had resolution of their IIH symptoms, and 97% of those with papilloedema were found to have resolution. The average postoperative ICP decrease was 25 cmH\textsubscript{2}O. Prospective, controlled studies are necessary [37].

The incidence of microcytic anaemia was found to be 10.3% in a review of 80 case notes. On correction of anaemia alone, the majority of these cases resolved [38].

A review of over 300 presumed IIH cases showed cerebral venous sinus thrombosis (CVST) was present in 11.4%. MRI alone identified 68% of CVST, with the addition of MRV revealing the other cases. Risk factors associated with CVST were only identifiable in 26% of patients [39].

Pseudotumour cerebri is described after successful surgery for Cushing’s disease. In a retrospective review of 941 surgeries, raised ICP was found in seven children (3%), but no adults, within 1 year of surgery and often while patients were still undergoing replacement steroid therapy. There was no correlation between the degrees of hypercortisolism before surgery [40].

In a review of Behcet’s disease patients with clinical evidence of neurological involvement, 6% of patients were found to have PTC [41]. There is also a recently published review of IIH in systemic lupus erythematosus [42].

Minocycline has been associated with mild and transient papilloedema due to raised ICP. However, two cases of severe papilloedema and visual field loss have now been reported. In these cases treatment of PTC had to be continued even after discontinuation of the minocycline [43].

**Conclusion**

Since the recognition of the condition there have been limited advances in evidence-based treatments for IIH, but myriad changes in proposed cause [44]: the publications in past months reviewed above have continued this bewildering tradition. The authors’ opinion is that weight gain is of fundamental importance and plays a causal role in IIH; the observation that weight loss ameliorates the condition supports this. Some of the articles reviewed above are at odds with this basic concept, suggesting that raised ICP may cause weight gain or that the pathogenesis of IIH may be from stenosis of a dural sinus with no explanation as to how this might be related to a high BMI except as a collision of two risk factors.

If normalization of the ICP is achieved (by whatever means) the condition will be cured. It is essential that this be brought about before irreversible visual loss has occurred. With so many potential therapeutic measures available—weight loss, acetazolamide and other carbonic anhydrase inhibitors, lumbo-peritoneal and ventriculo-peritoneal shunts and dural sinus stenting—the choice will depend upon, on the one hand, the risk of visual loss or of continued significant headaches if control of the ICP is not immediate, against the long-term complications of...
the various interventions. Unfortunately for our patients we still cannot advise them, based on class I evidence, which intervention is to be preferred and until such evidence is available decisions will continue to be based largely on local practice.

Acknowledgement
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References and recommended reading
Papers of particular interest, published within the annual period of review, have been highlighted as:

** of special interest
** of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 89–90).

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19 Kesler A, Kliper E, Shenkerman G, Stern N. Idiopathic intracranial hypertension is associated with lower body adiposity. Ophthalmology 2010; 117:169–174. It is often the interesting exceptions that prove the rule and this observation could also lead to a useful experimental approach to this question.
28 Further evidence, from a well designed prospective study, that weight loss is effective in inducing a remission in IIH.

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