Abstract

Introduction

Idiopathic intracranial hypertension (IIH) is a condition characterized by raised intracranial pressure (ICP) without hydrocephalus, space-occupying lesion and with normal cerebrospinal fluid (CSF) composition. Initially termed “serous meningitis”, this syndrome was first recognized by Quincke in 1897 [1].

At that time, he suggested that inadequate CSF resorption was responsible for the syndrome which is a theory that is still accepted by some researchers [2].

The term pseudotumor cerebri (PTC), commonly used interchangeably with IIH, was introduced by Nonne in 1904 who observed a condition characterized by clinical symptoms typically associated with intracranial tumors but with an unusual course of remission [3].

The diagnostic characteristics of this syndrome were first listed by Dandy in 1937 [4] and were later formulated into a set of diagnostic criteria (Modified Dandy Criteria) by Smith in 1985 [5].

These criteria have subsequently been updated by Friedman and Jacobson (Table 1) following advances in MR imaging and the discovery of other etiologies of intracranial hypertension e.g. venous thrombosis [6].

Other more specific criteria have been formulated for the diagnosis of PTC in the pediatric age group (Table 2).

Materials and methods

We retrospectively reviewed 9 cases diagnosed previously as “idiopathic intracranial hypertension” presenting to our Pediatric Department between the years 2005 and 2011. Institutional consent was acquired for this study. The children were reviewed in the clinics as part of their planned clinical follow up.

Results

Potential pathogenetic mechanisms were identified in seven of the patients ranging between growth hormone (r-GH) therapy, obesity, secondary hyperaldosteronism, cerebral venous sinus thrombosis, and cyclosporine therapy, however in two patients a specific mechanism was not identified. Response to any treatment was clinically and radiologically documented.

Conclusions

IIH in the pediatric age group may be due to a result of several potential risk and associative factors. These are reviewed with particular emphasis on management options and outcomes. More novel mechanisms have also been highlighted.

Introduction

Idiopathic intracranial hypertension (IIH) is a syndrome characterized by increased intracranial pressure (ICP) without hydrocephalus or space occupying lesion and with normal cerebrospinal fluid (CSF) composition. Initially termed “serous meningitis”, this syndrome was first recognized by Quincke in 1897 [1].
MR venography was traditionally reserved for investigating patients with an atypical sino-venous stenosis or occult venous thrombosis [18, 19]. Suspected intracranial hypertension in order to evaluate comprehensively for venous– sinus occlusions causing intracranial hypertension that may simulate IIH. Computed Tomography (CT) imaging can assess for hydrocephalus and space occupying lesions that have demonstrated reduced CSF drainage in IIH [33]. This is a more generally accepted hypothesis describing hampered outflow of CSF into the venous system as a cause of IIH. Venticular infusion studies (which monitor CSF dilution and calculate the rate of CSF overproduction) are invasive [27]. The only condition in which the CSF production rate is definitely known to be increased in patients with a choroid plexus papilloma, a rare pediatric tumor. However, an IIH-like syndrome has not yet been reported in a patient with choroid plexus papilloma. Idiopathic intracranial hypertension has also been associated with growth hormone therapy, a well-known risk factor, and this may be due to CSF hypersecretion. It is postulated that increased levels of IGF-I in the CSF during r-GH treatment may act on IGF-I receptors in the choroid plexus to increase CSF production [28, 29]. Even hypervitaminosis A has been linked to an increased production of CSF and a risk of pseudotumor cerebri [30]. CSF overproduction Intracranial hypertension may be secondary to excessive CSF production as first proposed by Quincke [1]. The production rate of CSF can be measured in patients, but the procedures required (infusion or perfusion techniques) are invasive [27]. The term "idiopathic intracranial hypertension" should be reserved to identify a "pure" condition, in which patients meet all the aforementioned criteria. The term "pseudotumor cerebri" however can be utilized to indicate a syndrome characterized by raised intracranial pressure, normal CSF contents, and normal brain with normal or small ventricles on imaging studies, even if an etiology may be demonstrated or supposed [22]. Pathophysiology Various mechanisms have been proposed for the etiology of Idiopathic intracranial hypertension, but the exact mechanism has yet to be fully elucidated. Most of the literature focuses on changes in CSF volume and in cerebral CSF hemodynamics, including increased cerebral blood flow, increased venous sinus thrombosis, and a reduced ventricular CSF opening pressure with IIH. papilledema is often identified at the time of presentation but is rarely observed on routine fundoscopic examination in asymptomatic patients [8, 9]. There are reports in the literature that describe patients, particularly in the pediatric age group, who are asymptomatic but have papilledema identified on routine fundoscopic examination in the investigation of IIH [12, 13]. The International Headache Society, in concordance with other published authors state that a patient diagnosed with IIH may have a normal neurologic examination, including aberrant papilledema [14]. Clinical symptoms such as seizures, focal neurologic deficits, altered level of consciousness and encephalopathy are typical of secondary causes of intracranial hypertension such as meningitis or cerebral venous thrombosis. These symptoms are useful in differentiating these conditions from IIH at the time of presentation. When the onset of symptoms is acute and the clinical course is progressive, a secondary cause should be suspected. Ophthalmoplegia can also occur in patients with IIH as a result of sixth cranial nerve palsy which is a false localizing sign [1]. Other patterns of ophthalmoplegia (i.e., third and fourth cranial nerve palsy, internuclear ophthalmoplegia) have also been reported in patients with IIH [15] but this is atypical and a secondary cause of intracranial hypertension, such as cerebral venous sinus thrombosis, should be strongly considered. Another important diagnostic criterion is the measurement of cerebro spinal fluid (CSF) pressure and the lumbar CSF opening pressure should be greater than 250 mm of water for a diagnosis of IIH to be made. This is measured with the patient in the lateral decubitus position with the legs extended and the patient as relaxed as possible [8]. Radiological findings Imaging is typically performed to exclude secondary causes of intracranial hypertension. Computed Tomography (CT) imaging can assess for hydrocephalus and space occupying lesions that can result in raised intracranial pressure whilst magnetic resonance imaging (MRI) is able to accurately assess for and exclude venous sinus thrombosis, meningeal infiltration and subarachnoid that are occult on CT imaging. MR venography further enhances the ability to investigate most symptomatic patients with venous– sinus occlusions causing intracranial hypertension that may simulate IIH [16, 17]. Many authors propose MR venography in addition to traditional MRI imaging for suspected intracranial hypertension in order to evaluate comprehensively for sino-venous stenosis or occult venous thrombosis [18, 19]. MR venography was traditionally reserved for investigating patients with an atypical presentation (eg, male, normal weight) in order to exclude sino-venous thrombosis. MR venography is more widely utilized in the investigation of patients with suspected elevated intracranial hypertension to evaluate for venous thrombosis or stenosis as the etiology of IIH symptoms. Developments of new imaging methods have enhanced detection of intracranial venous stenoses that were previously not appreciated on traditional time-of-flight MR venography. Some of the techniques currently used include 3D contrast-enhanced venography and a novel MR venography method using auto triggered elliptic centric ordered imaging [20, 21]. Supporting radiological signs of increased intracranial pressure in IIH include an empty sella, partially empty sella, flattened posterior orbital globe, enlarged pericerebral subarachnoid spaces, increased tortuosity of optic nerve sheath complexes, intracranial protrusion of the optic nerve head and slit-like ventricles [19]. To verify the Friedman and Jacobson criteria, a patient should undergo lumbar puncture with magnetic resonance imaging (MRI) of the brain and spinal cord and undergo an angiographic study of the intracranial vascular system. Idiopathic intracranial hypertension is a diagnosis of exclusion once other causes of raised intracranial pressure have been excluded. The term "idiopathic intracranial hypertension" should be reserved to identify a "pure" condition, in which patients meet all the aforementioned criteria. The term "pseudotumor cerebri" however can be utilized to indicate a syndrome characterized by raised intracranial pressure, normal CSF contents, and normal brain with normal or small ventricles on imaging studies, even if an etiology may be demonstrated or supposed [22].
The International Headache Society stated that a patient diagnosed with idiopathic intracranial hypertension may have a normal neurologic examination, including absence of papilledema [14]. Therefore, it should be considered in the differential diagnosis for all children that complain of headache, because it is likely to be an under-diagnosed condition.

We present in Table 3 the demographics, management profiles and outcomes of our 9 children [Table 3].

The treatment goals of IIH/PTC are relief of symptoms by normalizing CSF pressure and the prevention of loss of vision.

The most effective treatment modalities and the duration of therapy are yet to be elucidated. Acetazolamide is commonly used in the medical management of pediatric IIH. This drug is a carbonic anhydrase inhibitor which is thought to reduce the rate of CSF production and is generally used as the first line treatment [37].

In the patients in our series, Acetazolamide was used as first choice therapy in 6 patients and proved an effective treatment in 66% of our treated patients. This was prescribed orally at a dose of 20 mg/kg/day in 2–3 divided doses, until headache, disc swelling, and visual field abnormalities resolved which was typically within a 3–6 month period.

Common dose-related side effects of acetazolamide include gastro-intestinal disturbances, paresthesias involving the lips, fingers and toes, as well as anorexia and electrolyte imbalances.

Aldosterone exerts its biologic actions on epithelial cells of choroid plexus (rich of mineral corticoid receptor) by enhancing the activity and number of Na+ K ATPase pumps in their apical membrane.

Ouabain-sensitive Na+ K ATPase is present in the microvilli of the plexus and is involved in the regulation of CSF formation and electrolyte composition [Figures 1 and 2] [40]. As a result, spironolactone therapy has been recently proposed by some authors as a potential treatment option associated with primary and secondary hyperaldosteronism [41] especially in patients with chronic renal failure [38].

Also recombinant Growth hormone treatment in children with GH-deficiency can rarely lead to pseudotumor cerebi as occurred in two patients of our study group (Patient 1 and 4).

It has been reported that 22 children throughout the world who received r- GH for a variety of indications subsequently developed idiopathic intracranial hypertension [42]. A proposed mechanism of action is that GH passes the blood- brain barrier, acting locally to increase IGF-1 levels, which subsequently increases CSF production from the choroid plexus [43].

Another possible explanation is that in GH- deficient patients, recombinant GH treatment results in water and sodium retention which is associated with increased plasma rennin activity and plasma aldosterone levels, leading in turn to development of idiopathic intracranial hypertension through the mechanism outlined above.

The relationship between biosynthetic GH therapy and the risk of pseudotumor cerebi has resulted in some authors proposing octreotide as potential therapeutic agent.

Octreotide is a synthetic analogue of somatostatin and it has been observed that its administration resulted in remission of headache in patients suffering from idiopathic intracranial hypertension, lowering intracranial pressure (ICP) and with reversal of visual field defects [44].

Octreotide is a potent inhibitor of growth hormone and insulin-like growth factor-1, with its action mediated by somatostatin receptors subtype 2. The mechanism by which octreotide reduces intracranial pressure is still unknown. Somatostatin receptors (SSRs) have been detected in human choroid plexuses and arachnoid villi leading to the hypothesis that they might be related to cerebrospinal fluid production and absorption [Figures 1 and 2] [45].
Another recognized risk factor of IIH is obesity but the pathophysiological mechanism is still unknown. It has been suggested that pressure effects of centrally distributed adiposity elevates intra-abdominal pressure which subsequently elevates intra-thoracic pressure and cerebral venous pressure with subsequent raised intracranial pressure [48]. In our patient group there were 2 children with obesity that developed IIH. The first patient (patient n. 2) was overweight (BMI 31) but the second patient was morbidly obese (patient n.7) (BMI 41).

It's largely recognized that the risk of developing IIH (and also the severity of clinical picture) in the overweight pediatric population is not directly related to the degree of obesity [47]. The reason why only some obese patients develop IIH is still unknown. It is conceivable that the existence of an individual predisposition that may be related to either immunological (adipokines) or genetic factors (polymorphisms of chroid plexus receptors involved with the CSF production or dynamics). Also chronic steroid therapy can rarely lead to pseudotumor cerebri as occurred in one patient of our study group (patient 8) that had received corticosteroid therapy (oral budesonide 10 mg/day) over 6 months. There is a putative mechanism for the effects of corticosteroids on CSF production. The enzyme 1-hydroxysteroid dehydrogenase type 1 (11-HSD1) is highly expressed in the epithelium of the choroid plexus. among its main activities is the reduction of inactive cortisol to cortisone: the latter can activate mineralocorticoids with a degree of affinity similar to aldosterone increasing CSF pressure and leading in turn to the development of IIH, as recently suggested by some authors [52]. Of interest, it has been also proposed that autocrine regulation of intracerebral cortisol may represent a successful alternative option to CSF diversion procedures. However, the mechanism by which the stenosis occurs is unclear.

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**Conclusions**

IIH is a controversial neuro-ophthalmologic disorder of unclear pathogenesis although in some cases it is possible to elucidate a proposed etiology. In our series there were five potential pathophysiological causes (r-GH therapy, obesity, hyperaldosteronism, venous cerebral thrombosis, cyclosporine therapy) and IIH in children may be the result of several risk factors acting on an unknown individual predisposition.

On the basis of our results, derived from an effective response to unconventional therapies (spironolactone, octreotide), we suggest the use of these drugs in cases where a likely etiological factor has been recognized (hyperaldosteronism, r-GH therapy) as has been reported in isolated cases within the medical literature [41, 44]. These clinical results are promising and highlight the possibility of identifying the underlying pathogenesis of this disorder and help develop therapeutic interventions.

**References**

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