REVIEW ARTICLE

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Idiopathic Intracranial Hypertension and Associated Optic Neuropathy in Pediatric Patients

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ABSTRACT

While idiopathic intracranial hypertension (IIH) is more commonly recognized as a disorder of adults, it affects children of all ages and can have distinctive characteristics when presenting in the prepubertal age group. It is characterized by raised intracranial pressure (ICP) in the absence of brain parenchymal lesion, vascular malformations, hydrocephalus, or central nervous system (CNS) infection. The diagnosis is usually confirmed by a high opening pressure of cerebrospinal fluid (CSF) with exclusion of secondary causes of intracranial hypertension.

Objectives: The purpose of this review is to summarize relevant articles on the diagnostic tools used in evaluation and management of pediatric IIH. A summary of demographics, clinical presentation, diagnosis, neuroimaging, as well as existing evidence of treatment strategies is presented.

Method: We conducted a bibliographic search in PubMed using the terms idiopathic intracranial hypertension (IIH), Pseudotumor Cerebri syndrome (PTCS). The review of the literature revealed a lack of published consistent data on the diagnosis criteria and management of idiopathic intracranial hypertension in children.

Conclusion: This article provides a review of IIH in children and revised diagnostic criteria based on recent evidence and published opinion. Relative to the adult population, the demographic features and clinical presentation of IIH as well as the diagnosis and treatment guidelines for children are quite different. This review highlights the importance of early recognition and management of IIH to prevent permanent visual loss.

Key words: idiopathic intracranial hypertension, pseudotumor cerebri syndrome

INTRODUCTION

Idiopathic intracranial hypertension (IIH), also referred to as Pseudotumor Cerebri, is characterized by elevated intracranial pressure without discernable etiology, with normal cerebrospinal fluid content, and normal contrast-enhanced computed tomography (CT) or magnetic resonance irradiation (1,2,3).

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The current term used is Pseudotumor Cerebri syndrome (PTCS) or idiopathic intracranial hypertension (IIH). Other older names used during the last century were benign or primary intracranial hypertension and serous meningitis. While secondary PTCS is used when a potential cause can be identified, primary PTCS, or IIH refers to cases where all other possible causes have been excluded.

Unlike adults, in children secondary causes tend to be more frequent. General conditions, cerebrovascular anomalies, endocrine disturbances, infections, vitamins and prescribed drugs may cause PTCS in children, although the common mechanism is not fully known so far.

Over the last 30 years the prevalence of pediatric obesity has tripled. Yet, whether obesity or other putative IIH risk factors like the use of tetracyclines or retinoids for acne are more important in pediatric IIH is unclear.

The few studies that have examined the relationship between pediatric IIH and obesity have yielded conflicting results (4-9). The majority of studies so far suggested that obesity may be a risk factor for IIH only in postpubertal age children (4) as younger children with IIH are less likely to be obese or female, and it may be possible that IIH in this younger age group has a different mechanism.

The purpose of this review is to summarize relevant articles on the diagnostic tools used in evaluation and management of pediatric IIH, to review risk factors for pediatric IIH and estimate the magnitude of the association between overweight, moderate, and extreme childhood obesity and the risk of pediatric IIH.

Risk factors

It is unclear whether obesity and female sex are risk factors for pediatric IIH. Few studies have examined pediatric IIH risk factors and most are descriptive case series with BMI or weight information available only for some cases. Methodological limitations including small sizes (ranging from 15-50 cases with available weight data) lack of standardized definitions of pediatric obesity (which vary by age and sex), and referral center bias may explain the discrepancies between studies (10).

Age

The estimated incidence of IIH in the general population is of 1 case per 100 000. Cases have been described in children of all ages with a higher incidence in older children. It has been rarely diagnosed in babies and is almost inexistent in new-borns. Moreso, according to Babikian's study, 60% of children are over 10 years old (6).

Several studies suggest the puberty is an important milestone that separates children from adolescents in two different groups. In younger children PTCS does not correlate with neither sex nor obesity. As the onset of puberty is different in every individual, the presence of secondary gender characteristics is a better tool in defining the two groups than age (11-13).

Sex

Recent studies have shown that in younger children with IIH, nearly half are male, but in the older age group, the vast majority of patients are female (6). According to Balcer's study, there is a female preponderance in older children as 100% of patients between 15-17 were girls, while only 88% of those between 12 and 14, and 50% of those between 3 and 11 were females (4). These recent findings which associate obesity and female gender with IIH in older children suggest that in teenagers, risk factors for developing IIH might be similar to those in adults.

Overweight

Balcer et al. established that older children with IIH were more likely to be obese than younger children as 43% of patients aged 3–11 years were obese, whereas 81% of those in the 12- to 14-year age group and 91% of those in the 15- to 17-year age group met the criteria for obesity (4).

Alternatively, obese children with IIH may have been less common in older pediatric IIH studies because of a birth cohort effect (6). In recent studies, extreme obesity peaked at age 10 in boys, and girls had a bimodal peak at age 12 and 18 years (10). Even if obesity is a true risk factor for pediatric IIH, cohorts that were accrued before the pediatric obesity epidemic would be more likely to have a higher proportion of normal weight vs obese children with IIH presenting to their ophthalmology or neurology referral centers than cohorts accrued during the obesity epidemic. Because prior studies could not calculate risk estimates and included predominantly normal weight children in their base population, these case-only descriptions may have missed an association with childhood obesity (14).

Female sex and obesity first emerge as strong IIH risk factors in postpubertal age children. One of the most compelling results that links obesity to IIH comes from the study conducted by Sonu M Brara et al in 2012. According to their statistics, extremely obese adolescents were 16 times more likely than normal weight children to have IIH whereas moderately obese or overweight children were only 3.5-6 times more likely to have IIH, respectively (10). However, similar to previous studies they were not able to demonstrate a

clear association between obesity or female sex and IIH in prepubertal age children.

Novel findings suggest that the risk of IIH is highest among overweight/obese White non-Hispanic teenage girls (10).

While secondary causes for IIH are less commonly identified in adults, in 53–77% of pediatric cases there is an identifiable underlying condition. Reported associated conditions include endocrine abnormalities, medications (nalidixic acid, tetracyclines, nitrofurantoin, chemotherapies), viral infections (varicella, measles), nutritional etiologies (vitamin A toxicity, vitamin A or D deficiencies), or systemic conditions (Miller-Fisher syndrome, acute lymphocytic leukemia, Turner syndrome, galactosemia, galactokinase deficiency) (15,16).

Pathogenesis

The pathophysiologic mechanism(s) whereby obesity, particularly in postpubertal females, might lead to increased intracranial pressure is unknown. Based on findings that the risk of IIH increases dramatically in postpubertal age girls particularly right around the time of menarche, it is tempting to speculate that menstrual cycle hypothalamic-pituitary-ovarian axis hormones play a role (17).

However, it may be that these girls had rapid weight gain around the time of menarche and that this better explains the sudden increase in IIH risk.

Diagnosis

The diagnosis of IIH in children is one of exclusion, as central nervous system neoplasms may present with similar symptoms (18,19).

While headache, nausea, and vomiting are classic symptoms of IIH, patients may also complain of blurred vision, double vision due to cranial nerve palsies, and stiff neck. Children can describe visual symptoms including transient visual loss, photophobia, and 'shimmering lights with colored centers'. Patients with IIH have normal levels of consciousness and functioning (10).

Patients and parents should be asked whether the child has had any recent weight gain, has taken medications associated with IIH (tetracycline, chronic steroids recently tapered, synthetic GH), or has an underlying medical condition associated with IIH. Development of secondary sexual characteristics should also be recorded. The child should be asked whether he or she has visual symptoms, headache, nausea or vomiting, neck or back pain, or any other neurological complaints (20).

Headache is the main complaint among children with IIH and has been documented in 62-91% of cases. There are also reports of IIH without headache symptoms either because the child is too young to articulate or because headaches are absent (15,20). The reason for lack of headache despite increased ICP is unknown. Children with IIH but without headaches, tend to have more neurological signs and vision loss at presentation and a poorer prognosis. The headaches may be a warning sign before vision loss occurs and aggressive reduction of ICP and treatment of papilledema is critical (21).

Prepubertal children with idiopathic intracranial hypertension most commonly present with strabismus, which resolves rapidly with the initiation of treatment.

Visual loss has been reported to occur in children with idiopathic intracranial hypertension and visual field defects are usually present in all eyes. The most common defect in patients with idiopathic intracranial hyper-tension is an enlarged blind spot, which has been reported to occur in virtually all eyes with papilledema (2).

Children with suspected IIH should have a careful neurologic and ophthalmologic examination, performed by a neuro-ophthalmologist detailing visual acuity, color vision, pupillary examination, ocular motility, visual fields and dilated ophthalmoscopy.

Papilledema, ranging from mild blurring of the disc margins to gross disc swelling with hemorrhages and exudates, has been regarded as a hallmark finding of IIH. The disc edema is generally bilateral, but it can be asymmetric or unilateral. Papilledema in children resolves after 3-6 months of medical treatment, but in some cases last for several additional months. In infants with open sutures, papilledema may be absent In patients without papilledema, there is generally no threat of vision loss and treatment is primarily symptomatic headache management (9,16,22).

Normal neuroimaging studies are mandatory before diagnosing pediatric IIH and performing a lumbar puncture (*table 1*)(23-25). Since conditions with meningeal infiltration or cerebral venous sinus thrombosis (CVST) can mimic pediatric IIH and may be missed by CT, MRI of the brain with and without gadolinium for detecting meningeal or intraparenchymal lesions and MR venography (MRV) are the studies of choice for diagnosis of CVST (26,27).

Magnetic resonance imaging (MRI) can be used to predict the presence of elevated intracranial pressure. A constellation of brain MRI signs (flattening of the posterior sclera, empty sella, distension of the perioptic subarachnoid space, enhancement of the prelaminar optic nerve, vertical tortuosity of the orbital optic nerve, and protrusion of the prelaminar optic nerve) can assist in establishing the diagnosis (28).

After normal neuroimaging, a lumbar puncture is critical to measure the CSF opening pressure and

Table 1 - Proposed diagnostic criteria for prepubertal IIH
[adapted from Rangwala and Friedman (23,24,25) (Rangwala LM, 2007;) (Friedman DI J. D., 2004)(Friedman DI L. G., 2013)]

1. Papilledema;
2. Normal neurologic examination except for cranial nerve palsies or signs that reflect generalised intracranial hypertension*; normal mental status;
3. Brain imaging: normal brain parenchyma, without hydrocephalus, mass or vascular lesion and no abnormal meningeal enhancement or venous sinus thromobosis on MRI ** (with and without contrast) and MR -venography; narrowing of transverse sinus is allowed;
4. Elevated CSF opening pressure in a properly performed lumbar puncture in lateral decubitus position (age appropriate): neonates >76 mm H2O; age 1-18 years > 280 mmH20;
5. Normal CSF composition except in neonates who may have up to 19 WBC/mm^3 if 0-28 adys and up to 9 WBC/mm3 if between 29 and 56 days; protein is acepted up to 150 mg/dl

*in the absence of an identifiable etiology and if improved with reduction of cerebrospinal fluid pressure or resolution of other signs of intracranial hypertension
** if MRI is not available or cotrnaindicated contrast-enhanced CT can be used
The diagnosis of IIH is definite if 1-5 are met and is probable if 1-4 are fulfilled but CSF opening pressure is lower than specified.

to exclude meningitis. A lumbar puncture should be performed in the lateral decubitus position with the legs flexed, using mild sedation when necessary, and measuring the opening pressure with a standard manometer. Based on the first prospective study assessing the CSF opening pressure reference ranges in 165 children, 280 mm H2O should be used as the normal opening pressure for patients between 1 and 18 years of age (29,30). More recently, the 90th centile of CSF pressure on lumbar puncture has been reported to be 280 mm H2O (22 mmHg) in children aged 7 to 18 years, without a significant age effect (25). Cerebrospinal fluid reference ranges in neonates are different compared to values in young children. In normal neonates, a value above 76 mm H2O is considered an elevated CSF opening pressure (31). More recent studies in infants and children with intracranial pressure monitoring report an upper limit of normal as 135 mm H20 (10 mmHg) between the ages of 2 years and 5 years; with adult levels of CSF pressure being reached by 8 years of age.

While for infants aged ≤ 28 days, a cell count above 19/µl is considered elevated, the value for infants ages 29–56 days is greater than 9/µl (32)CSF protein can be relatively elevated in neonates (up to 150 mg/dl), but will decline to normal levels (15–45 mg/dl) after the first 6 months of life (33).

In adults and children the assessment of average CSF pressure over more than 20 minutes, 'steady state', is reported to be more reliable than a single opening pressure measurement using the height of a fluid column (34-36).

Other Investigations

Patients in whom the intracranial hypertension is not truly idiopathic but has an identifiable etiology (otitis media, dural sinus thrombosis, systemic lupus erythematosus, neck injury, metastatic disease, nephrotic syndrome or arteriovenous malformations) should be excluded.

Treatment

Treatment is empirically dictated by the level of vision loss and severity of headache. Toxic, metabolic, and nutritional causes must be promptly addressed, and weight loss must be encouraged in children who are overweight. A weight loss of 10% less than the child's weight at diagnosis is recommended (37). Repeat lumbar punctures are discouraged by most experts because they are painful, poorly tolerated in young children, who often require sedation, and have short-lived effects as the drained spinal fluid is replenished in a day (38).

Most cases of pediatric IIH respond to medical management; thus, surgical management is typically reserved only for those who fail medication. In rare instances, patients may respond to one spinal tap with resolution in papilledema without the need for additional therapy.

Medical Management

IIH can cause permanent vision loss in up to 10% of children and severe headaches that may persist even after intracranial pressure is normalized (9).

Acute treatment of IIH includes mild diuretics like acetazolamide, serial lumbar punctures, or if necessary, lumbo-peritoneal shunts or optic nerve sheath fenestratations. In situations of acute, severe visual loss, the combination of oral or IV acetazolamide and IV methylprednisolone 15 mg/kg can be used when surgery is not immediately available. The use of chronic steroids, however, should be avoided (39).

Acetazolamide or furosemide are commonly used in the medical management of pediatric IIH. Acetazolamide, a carbonic anhydrase inhibitor, is thought to reduce the rate of CSF production, and is generally the first-line treatment. Doses are 15 mg/kg/day in 2–3 divided doses, until headache, disc swelling, and visual field abnormalities resolve – typically in 3-9 months. Common dose-related side effects include GI upset, paresthesias involving the lips, fingers, and toes, anorexia, and electrolyte imbalance (metabolic acidosis). Electrolytes are usually not monitored, as children are usually asymptomatic from the acidosis. When the side effects become intolerable, the dose is lowered or acetazolamide is

replaced or combined with furosemide (0.3–0.6 mg/kg /day) (40).

Topiramate (1.5–3.0 mg/kg/day in two divided doses, and no more than 200 mg/day) may be used as a second-line agent, particularly when the child is obese. Topiramate, an antiepileptic medication, has secondary carbonic anhydrase activity. Topiramate use in IIH is relatively new and has the added benefit of appetite suppression and weight loss in many patients. It is an excellent medication for chronic daily headache and it has been used safely for years in children with epilepsy. The dosage should be increased slowly over weeks (25 mg/week) to reduce the risk of cognitive side effects, which are more common with rapid dose escalations and at doses ≥200 mg/day (41,42). If topiramate is not tolerated, zonisamide, also with carbonic anhydrase activity and appetite suppression, may be used.

Although the optimal duration of treatment is unknown, some experts recommend that treatment is continued for at least 6 months after visual status, and optic nerve appearance stabilize before tapering off medications (43). Chronic management focuses on symptomatic treatment of headaches and weight loss counseling to mitigate the 6%-22% risk of recurrence (44). During the acute phase, it is recommended that children should be examined by an ophthalmologist at least monthly.

Surgical treatment

Surgical procedures, such as optic nerve sheath fenestration (ONSF) and CSF shunting can be considered when medical treatment fails. Optic nerve sheath fenestration (ONSF) is indicated in cases of acute, severe or progressive vision loss despite medical treatment (9). It is performed by making an incision in the optic nerve sheath, which improves CSF drainage and decreases the pressure on the optic nerves. About 50% of patients who underwent surgery on one side reported bilateral improvement in visual acuity (9). The complication rate of this procedure ranges from 4.8% to 45%, with a mean of 12.9% The most commonly reported complications are diplopia, anisocoria, and corneal drusen. Rarely central retinal artery occlusion, acute angle closure glaucoma, and optic neuropathy may occur (45-47).

Most commonly used CSF shunting procedures are lumboperitoneal (LP) and ventriculoperitoneal (VP) shunts. LP shunt has been reported to be the most successful in alleviating patient symptoms (48). Complications of LP shunt include shunt obstruction, lumbar radiculopathy, infection, and tonsillar herniation (9,49,50).

Transverse sinus stenting may be an alternative treatment option in patients with refractory IIH who fail medical treatment (51).

Interestingly, in morbidly obese IIH children with unsuccessful trials of weight loss, bariatric surgery can be considered with positive effects. This is also indicated if obesity is associated with other complications other than IIH, such as diabetes or sleep apneas (52,53).

CONCLUSIONS

Idiopathic intracranial hypertension is a very rare disorder and frequently misdiagnosed in children and adolescents. Presentation under 10 years and/or weight under the 90th centile is exceptional. In these situations extreme caution before diagnosis is recommended. Particular care should be taken to look for causes of secondary IIH.

Opening CSF pressure using a manometer alone can be inadequate, noting the proposed revised upper range. Steady state CSF pressure assessment, in a relaxed and comfortable child, rather than measuring CSF opening pressure, in centimetres of water, may be helpful. In true IIH, expert opinion on high-quality MRI and MRV is often helpful (54).

Papilledema associated with idiopathic intracranial hypertension (IIH) may result in irreversible, progressive visual loss. The development of tools for the evaluation of pediatric patients with IIH is particularly relevant as many patients may not be able to comply with the detailed clinical evaluation utilized in adults for the treatment and management of this disease. Children with this rare, challenging disorder benefit from an expert, multidisciplinary pathway/team.

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