International Journal of Immunopathology & Pharmacology

Letter to the editor

International Journal of Immunopathology and Pharmacology
2017, Vol. 30(1) 94–97

DOI: 10.1177/0394632016681578
journals.sagepub.com/home/iji
SAGE

Therapeutic approaches to pediatric pseudotumor cerebri: New insights from literature data

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Abstract

The pseudotumor cerebri syndrome (PTCS), also known as idiopathic intracranial hypertension (IIH), is characterized by signs and symptoms of increased intracranial pressure such as headache and cranial nerve palsies, in the absence of any space-occupying mass. This condition commonly affects overweight women of childbearing age, even if it is also frequent in men and children. Children with PTCS may present with atypical signs and symptoms, with a different prognosis compared to adults. However, the treatment is the same for both children and adults, even if there are no strict treatment guidelines in regards. All treatment strategies in children are based on retrospective studies and none has been evaluated in prospective or randomized controlled trial studies. This review focuses on literature data on PTCS treatment in children.

Keywords

pediatrics, pseudotumor cerebri, treatment strategies

Date received: 31 August 2016; accepted: 7 November 2016

Introduction

Pseudotumor cerebri syndrome (PTCS), also known as idiopathic intracranial hypertension (IIH) is characterized by signs and symptoms of increased intracranial pressure without evidence of intracranial mass or vascular lesions. Increased intracranial pressure can cause headache, pulsatile tinnitus, nausea, vomiting, blurred vision, and transient visual loss.

IIH is a misnomer since a small percentage of PTCS patients have an identifiable secondary cause such as cerebral venous abnormalities, use of some antibiotics, vitamin A and retinoids, and some medical conditions, including meningitis, dural venous sinus thrombosis, systemic lupus erythematosus, leukemia, and kidney failure.[1] Literature data have also described some syndromic conditions of PTCS, suggesting the hypothesis of a genetically mediated

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pathology.[2,3] Specific surveys showed that alteration of the endocytosis processes could be attributed to high levels of cellular oxidative stress, which contribute to the pathogenesis of many degenerative and progressive neurological diseases.[4]

Definite PTCS is considered in a patient presenting with papilledema (the hallmark of PTCS), plus normal neurological examinations except for cranial nerve abnormalities, normal neuroimaging—no intracranial masses or hydrocephalus—normal cerebrospinal fluid (CSF) composition, and elevated lumbar puncture (LP) pressure. Probable PTCS is defined when the LP pressure is lower than what is expected for a definite diagnosis. LP is considered high when CSF $\geqslant$250 mm in adults and $\geqslant$280 mm in children (CSF of 250 mm if the child is not sedated and not obese). Some patients do not have papilledema, but show increased intracranial pressure plus sixth nerve palsy. When papilledema and sixth nerve palsy are not present, elevated intracranial pressure with at least three of the following neuroimaging criteria should be met: empty sella, flattening of the posterior aspect of the globe, distention of the perioptic subarachnoid space with or without a tortuous optic nerve, and transverse venous sinus stenosis.[1]

Pediatric PTCS was first defined in patients aged less than 18 years. However, puberty was proposed as an important physiological factor in the incidence and pattern of PTCS; thus, pediatric PTCS was further divided to pre-pubertal (pediatric) and pubertal (adolescent).[5] The pediatric (prepubertal) group is classified as a different group due to fewer associations with obesity and female gender compared to the pubertal group.[5] However, as a general rule, obesity plays an important role in PTCS in children similar to what is seen in adults.[6] Any child, presenting with a new-onset headache or visual problems should be considered as a PTCS case irrespective of age, gender, weight, or other predispositions. A pediatrician, neurologist, ophthalmologist, otolaryngologist, and sometimes neurosurgeon should be involved in the treatment of these patients. The goal of treatment in PTCS is alleviating the symptoms of increased intracranial pressure and preventing visual loss. Nevertheless, there is a lack of randomized clinical trials in pediatrics and most patients are managed based on medications and approaches used in adults. Therefore, the focus of our paper is to analyze current therapeutic strategies efficient in resolving PTCS in childhood, in order to draft some guidelines useful in this age group.

Materials and methods

In this study, we focused on the treatment options, described in literature up to date, for PTCS in the pediatric population. We searched for pseudotumor cerebri and idiopathic intracranial hypertension in the pediatric population in Google Scholar, Medscape, Scopus, and PubMed. Our keywords were "pseudotumor cerebri," "idiopathic intracranial hypertension" (and other relevant keywords) focusing on "treatment" and "children" or "pediatric" studies. For clinical trials, we searched clinicaltrials.gov. We included case reports, case series, and cross-sectional studies as well as retrospective or prospective studies and clinical trials with a focus on pediatric studies. After recruiting some articles, we performed a manual search on the reference lists from review articles or other articles that were found. English articles or those with English abstract were included in this study. The search was performed by two independent authors and combined for article writing. Efforts were made to access the full texts of articles through contacting the corresponding authors when needed.

Results

When evaluating the treatment options of pediatric PTCS, the etiology of the condition should also be found and removed or treated. Medical management is the first step and surgical intervention is reserved for patients with a severe headache, progressive or significant visual loss, and when medical treatment fails.

For some patients with normal vision and mild papilledema, no treatment is required and patients are only observed.[7] For others, the first LP that is performed for diagnostic approaches might also be therapeutic with no need for any other treatment. Serial LPs either alone or with medication are useful for some patients as well.[5] This has not been confirmed in randomized clinical trials, though. In those requiring medical treatment, similar to adult patients, the first line treatment is acetazolamide, a carbonic anhydrase inhibitor that functions through decreasing the secretion or production of CSF from

choroid plexus. In children, the standard dosage is 15–25 mg/kg/day three or four times daily. With regards to symptoms, dosing can be increased up to 100 mg/kg—a maximum of 2 g/day in children and 4 g/day in adolescents.[8] There is no randomized controlled trial in pediatrics, but the Idiopathic Intracranial Hypertension Treatment Trial (IIHTT) has evaluated the use of acetazolamide plus weight reduction and/or low sodium diet versus diet plus placebo in IIH patients with mild visual loss aged 18–60 years in a 12-month intervention phase and 3-year follow-up. Based on this study, acetazolamide use was consistent with improvements in papilledema and visual acuity and vision-related quality of life.[9]

In a prospective study of 36 pediatric patients, symptoms were resolved in four patients with removal of the identifiable predisposing cause (middle-ear infection, obesity, vitamin overdose, medications, etc). Of the 17 patients, eight were effectively treated with acetazolamide and 22 of 24 patients were treated with acetazolamide and corticosteroid therapy. Two patients had permanent vision loss.[10] In a study of 23 pediatric patients, three were treated with a single LP. Acetazolamide therapy alone cured four cases in 2–4 weeks.[11] In a retrospective study of 18 children, two patients were treated only with LP and 11 out of 15 cases were effectively treated with acetazolamide as the first line treatment. Corticosteroids were used as the second line treatment in the four patients who failed to respond to acetazolamide and as first treatment in another four patients. Six treatments could be analyzed and corticosteroids were effective in five patients. Researchers concluded that the dosage of acetazolamide should be increased to avoid the use of corticosteroids in these patients.[12]

For those patients who do not respond to acetazolamide, the next line of treatment is furosemide or corticosteroids. Furosemide is a loop diuretic that inhibits carbonic anhydrase inhibitor. For children, it is administered 1–2 mg/kg/day to 2 mg/kg three times daily.[13]

The efficacy of combined therapy with acetazolamide and furosemide in children with PTCS was evaluated in a case series of eight children. Patients were treated orally with these two drugs (acetazolamide: 37–100 mg/kg/day, and furosemide: 1 mg/kg/day) until papilledema cleared. Patients had a significant reduction in their intracranial pressure after 1 week of treatment and the intracranial pressure went back to normal after 6 weeks.[13]

The next line of treatment includes corticosteroids, which are used as short-term therapy for acute attacks, but not recommended for long-term treatments due to side effects.

Topiramate was shown as efficient in treating PTCS given its effects on carbonic anhydrase, which help to decrease the CSF production. An open-label study in adult PTCS patients reported no significant difference between acetazolamide and topiramate.[14] Recently authors have suggested that lipophilic carbonic anhydrase inhibitors such as methazolamide, zonisamide, or topiramate might be more effective than acetazolamide.[14] Topiramate has also been proposed when acetazolamide is not effective.[14]

Serial LPs (twice weekly) have been proposed for patients that do not respond to medical management, but refused surgical treatment for any reason. However, this strategy is not favorable in children, considering the technical challenges in obese patients, as well as pain and agitation in children.[15] Finally, mechanical non-invasive ventilation has been proposed in those cases associated with increased serum levels of $PaCO_2$, considering its effect in the reduction of serum concentrations of this gas and its diffusion into the central nervous system via the blood–brain barrier.[16]

Surgical intervention is reserved for patients with rapid fulminant visual loss or progressive visual loss or chronic headache despite adequate medical treatment that occurs in about 20% of PTCS patients.[7] One surgical intervention is optic nerve sheath decompression that has been applied in children for acute and severe visual loss. For refractory cases that do not respond to optic nerve sheath decompression, CSF shunting is the next line of treatment.[8] CSF shunting routes include lumboperitoneal shunting, ventriculoperitoneal shunting, and shunts from cisterna magna. Endoscopic optic nerve fenestration is another strategy that has been used in children, with evidence to be an effective minimally invasive procedure. These two methods may not be comparable due to different types of patients and severity of clinical presentations in these treatments.[8] Visual outcomes after these interventions has been reviewed, yielding 49.3%, 56.6%, 67.2%, and 84.6% improvement in patients following ventriculoperitoneal shunt,

lumboperitoneal shunt, optic nerve sheath fenestration, and dural venous sinus stenting, respectively,[8] even though it should be considered that CSF shunting has complications of its own: shunt obstruction, infections, need for revision, or CSF leak.

This review shows that although different medical and surgical strategies are used in pediatric PTCS, there are no strict treatment guidelines on how to treat them. None of these strategies has been exclusively evaluated in children. Therefore, further clinical trials, prospective, retrospective, and cross-sectional studies are mandatory to evaluate the efficiency and safety of treatment options in pediatric PTCS.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

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