Pseudotumor Cerebri Syndrome in Children: Current Diagnosis and Treatment

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9.1 Introduction

Suspicion of papilledema or swelling of the optic nerves from elevated intracranial pressure (ICP) is a common reason for referral to pediatric neuro-ophthalmology. The pediatric neuro-ophthalmologist is tasked with confirming the presence or absence of papilledema and if present, determining the next steps in evaluation and management. Increased ICP, in the absence of a mass, has been labeled pseudotumor cerebri syndrome [1–4]. This designation encompasses idiopathic intracranial hypertension (IIH; used interchangeably with primary pseudotumor cerebri syndrome in this chapter) as well as elevated ICP secondary to etiologies including exposure to certain medications, in association with underlying systemic disease, and cerebral venous system abnormalities. This chapter outlines the epidemiology, pathophysiology, and etiologies of pseudotumor cerebri syndrome (PTCS). Further, this chapter reviews the most recent diagnostic criteria, disease monitoring methods, treatment approaches, and visual outcomes for PTCS. Having a systematic strategy in place to evaluate patients with papilledema and presumed pseudotumor cerebri is crucial for the timely identification of an underlying etiology, if present, and for the prevention of visual loss with effective treatment.

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9.2 Epidemiology

The incidence of IIH in the pediatric population (<18 years of age) has been estimated at 0.63–0.90 per 100,000 children [5–7]. This is similar to estimates for IIH in the general adult population estimated at 0.9 per 100,000 [8]. Within the traditional IIH demographic of obese women aged 20–44 years, the incidence rises to 19.3 per 100,000 [8]. By contrast, the demographics of pediatric IIH vary depending on age and pubertal status. There is a predilection for obese females in the pubertal population, but prepubertal children demonstrate equal proportions of male and female patients [4]. Notably, these estimates do not include cases of secondary pseudotumor cerebri syndrome, only those of an idiopathic etiology.

The interplay between pubertal status and obesity in the incidence of IIH has been highlighted in several studies. Tepe et al. performed a prospective study where the authors performed ophthalmologic exams on 1058 obese children, uncovering 14 cases of IIH (prevalence of 1.3%). Considering pubertal status as defined by Tanner stage, the prevalence among postpubertal subjects was 1.5% vs. 0.9% in prepubertal subjects [9]. Sheldon et al. performed a multicenter retrospective review of 233 pediatric IIH cases. While they found associations between age and body mass index (BMI) in both boys and girls, the likelihood of obesity among patients increased when among those diagnosed at age 12 on average [10]. They highlighted three specific subgroups of pediatric patients: a preadolescent group that was younger and had no association with weight, an early adolescent group that tended to be overweight or obese, and a late adolescent group that tended to be more obese similar to the adult phenotype [10]. These anthropomorphic features of pediatric IIH are corroborated by other studies demonstrating that obesity is a risk factor for IIH in and after puberty [11, 12]. Brara et al. found that among children between the ages of 11 and 19, the risk of developing IIH was much higher in overweight and obese children [13]. While these studies agree that the important risk factor of obesity depends on age, and/or pubertal status, only a prospective study with detailed pubertal staging will allow us to reliably define the anthropomorphic features of pediatric IIH.

The important role of pubertal status in governing the prevalence and features of IIH intuitively suggests a potential hormonal role in IIH pathogenesis. Notably, endocrine disorders such as Addison's disease, hypoparathyroidism, adrenal insufficiency, and hypo/hyperthyroidism as well as exogenous growth hormone use have been associated with secondary pseudotumor cerebri syndrome [1, 3, 14, 15]. Tepe et al. found that 14 obese patients with IIH had evidence of metabolic syndrome, including transaminitis, evidence of insulin resistance, elevated cortisol, and fasting insulin levels [9]. Cerebrospinal fluid production may be influenced by metabolic and hormonal signaling [16, 17], suggesting a potential direct role for hormonal dysregulation in intracranial hypertension. However, no single hormonal factor has been identified as causative in pediatric or adult IIH. Future research in this area is warranted which could potentially enable the identification of at-risk individuals by serologic testing.

9.3 Symptoms

Symptoms of pseudotumor cerebri syndrome reflect those secondary to elevated ICP including headache (often positional), transient visual obscurations, pulsatile tinnitus, and binocular diplopia. While the spectrum of symptomology is similar between children and adults, pediatrics poses added diagnostic challenges in teasing out these symptoms. Depending on patient age, the children may not be able to specifically or accurately express symptoms as well as their adult counterparts. As such, the predictive values of typical symptoms are lower in children than in adults.

Pediatric patients may present without the classic symptoms of elevated ICP. Aylward et al. performed a retrospective review of 152 patients with pseudotumor cerebri syndrome and found that 14.5% did not endorse headaches [18]. This group was younger (mean age 9.7 without headache vs. 13.4 years with headache) and less likely to be overweight or obese. Importantly, cerebral spinal fluid opening pressures on lumbar puncture were not different between these groups [18]. Among patients with secondary pseudotumor syndrome in this study, 35/37 patients (95%) reported headaches. The authors did not specifically comment on the age of patients with secondary pseudotumor cerebri and if that may have influenced symptomology. Glatstein et al. retrospectively evaluated patients younger than 17 who presented to a tertiary care hospital emergency department over an 8-year period and were subsequently diagnosed with IIH. Of the 63 patients that were identified, 47(75%) presented with headaches. Headache was less common in children <11 years of age compared to those in the 11–17-year-old group [11]. Thus, headache is less commonly reported among pediatric patients with pseudotumor cerebri syndrome, particularly among younger children.

Pediatric patients may present entirely without symptoms. In their study, Ayward et al. noted that 8/22 (36%) patients were referred because of incidental discovery of papilledema during a routine eye exam [18]. Bassan et al. evaluated 45 pediatric patients with IIH and found that 14 (31%) were asymptomatic. As in the aforementioned studies, asymptomatic patients were younger and less likely to be obese. They also noted a male predominance (10/14, 71%) in the asymptomatic group [19]. A retrospective review of 86 patients with PTCS at Boston Children's Hospital found that 21% were asymptomatic. Asymptomatic patients were more likely to be younger and have lower body mass indices compared to symptomatic patients [20]. Thus, the literature is consistent in showing that a significant population of IIH patients are asymptomatic (may be discovered incidentally) and that these patients tend to be younger.

Secondary pseudotumor cerebri patients can also present with or without symptoms. To our knowledge, no study has examined potential differences in symptomology between primary and secondary pseudotumor cerebri syndrome specifically in children. Orme et al. evaluated adult patients with pseudotumor cerebri syndrome secondary to tetracycline use and compared the clinical features to traditional IIH patients. They found that patients with tetracycline-induced pseudotumor cerebri were less likely to be obese (43.8% vs. 79.2%) and were more likely to present with

double vision [21]. There was no statistically significant difference in the rate of headaches reported at presentation between the two groups. The disease course was shorter in the secondary pseudotumor cerebri patients (mean duration of 18.3 weeks vs. 62.9 weeks) and the risk of recurrence was higher in the IIH group (16.5% vs. 4.0%) [21]. Liu et al. evaluated 65 patients of all ages who presented with cerebral venous sinus thrombosis and found 87.7% of patients presented with headache and 23.1% with pulsatile tinnitus [22]. As mentioned previously, Aylward et al. included 37 pediatric patients with secondary pseudotumor cerebri syndrome and 35/37 (95%) had headache on presentation. Secondary pseudotumor seems more likely to present with headache in children but this is an area that needs further explanation as it has not been evaluated based on age or pubertal status in children [18]. Clinicians should have a high index of suspicion for secondary causes in prepubertal patients who present with symptoms of elevated ICP.

9.4 Diagnosis

9.4.1 Examination

Findings on ophthalmic examination of pediatric patients are identical to those of adults with pseudotumor cerebri syndrome, including papilledema with or without afferent visual dysfunction (decreased vision, visual field defects, and dyschromatopsia) and abduction limitations with esotropia (Figs. 9.1 and 9.2) [1, 3]. Comprehensive neuro-ophthalmic examination and testing are essential in the evaluation of suspected elevated ICP so that more malignant presentations can be identified. For example, patients presenting with fulminant IIH are at risk for serious visual morbidity if not treated quickly and aggressively [23]. Fulminant IIH is defined as an acute development of symptoms of increased ICP with rapidly progressive vision loss within 4 weeks of symptom onset and in the setting meeting clinical criteria for IIH. Thambisetty et al. described 16 cases of fulminant idiopathic intracranial hypertension in patients ranging in age from 14 to 39 who presented with acute symptoms (mean onset 16.1 days) and suffered subsequent irreversible vision loss within 4 weeks of symptom onset. Aggressive interventions included multiple lumbar punctures, and optic nerve sheath fenestration or CSF diversion in 11/16 patients. Despite these measures, all were left with severe, bilateral visual field deficits and 8/16 (50%) remained legally blind [23].

Although papilledema ICP is a hallmark ICP examination finding, its absence does not preclude the diagnosis of pseudotumor cerebri syndrome [1]. A subset of pediatric patients with PTCS may present without papilledema, just as in adults. Aylward et al. noted that 27/152 (17.8%) patients in their retrospective review did not have papilledema. Comparing features of those with and without papilledema, they found no differences in age, body mass indices, or opening pressure on lumbar puncture [24]. Glatstein et al. reported a similar proportion (12/63, 19%) of IIH patients presenting to the emergency department did not have papilledema. Patients with secondary pseudotumor cerebri syndrome can also present without

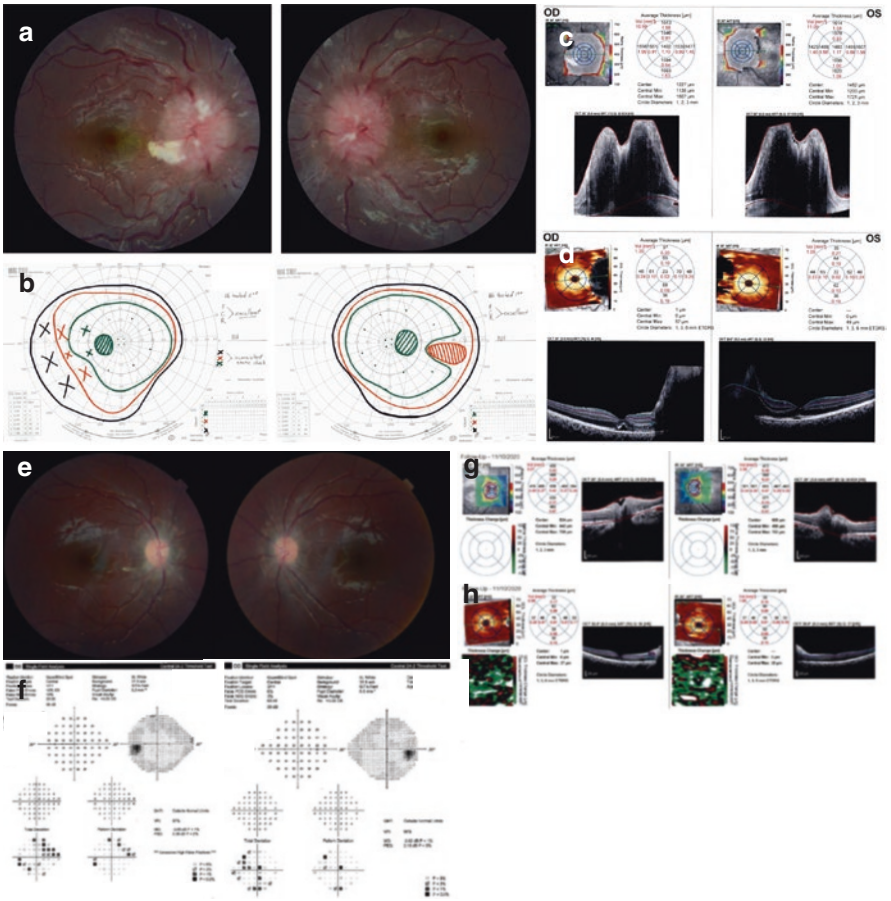

Fig. 9.1 This is a representative case of a 14-year old obese African American female who presented with 3 weeks of progressive headaches and one episode of vomiting. She reported that the headaches would wake her from sleep at times and transient visual obscurations. MRI brain without contrast and MRV were notable for protrusion of the optic nerve head papillae into the globes in both eyes, distention of the optic nerve sheaths, and a partially empty sella. Lumbar puncture with opening pressure revealed bland constituents and an opening pressure of 36 cm H_2O. Visual acuity, pupils, and color vision were normal. She had grade 5 papilledema in both eyes with cotton wool spots. (**a**) She was unable to accurately take an automated perimetry test and kinetic perimetry revealed enlarged blind spots in both eyes. The right eye had a temporal scotoma that was felt to be an extension of the enlarged blind spot (**b**) Her optic nerve head volume was unable to completely capture the degree of swelling. (**c**) Her ganglion cell layer was unable to be properly segmented given the swelling and she had subfoveal fluid in both eyes as well as cystic intraretinal edema in the right eye. (**d**) She was treated aggressively with acetazolamide which was increased to 2 g total per day (24.8 mg/kg/day). She developed a significant and symptomatic metabolic acidosis and was started on sodium bicarbonate supplementation. She was monitored initially twice weekly and then this was slowly spaced out as a concern for vision loss dissipated. On follow-up 2 months later, her optic disc edema had essentially resolved and she was left with significant gliosis in both eyes (**e**). Her visual acuity, color vision, and pupils remained normal. She improved on her ability to take automated visual fields and now there were only scattered nonspecific defects though the left eye reliability was borderline. (**f**) Her optic disc edema had dramatically improved and her optic nerve head volume had returned to essentially normal. (**g**) Her OCT GCL was now low normal indicating some ganglion cell layer loss that was not visually significant (**h**)

papilledema. Liu et al. performed a retrospective multicenter evaluation of adult and pediatric patients with cerebral venous sinus thrombosis and found that only 35/65 (54%) presented with papilledema, though it later manifested in the remainder of patients [22]. Thus, the absence of papilledema should not be considered as an exclusive feature in the diagnosis of pseudotumor cerebri.

The presence of pseudopapilledema can raise concern for and even confound a diagnosis of pseudotumor cerebri syndrome [25]. Pseudopapilledema, caused by optic nerve head drusen and hyperopia, for example, commonly drive referrals to

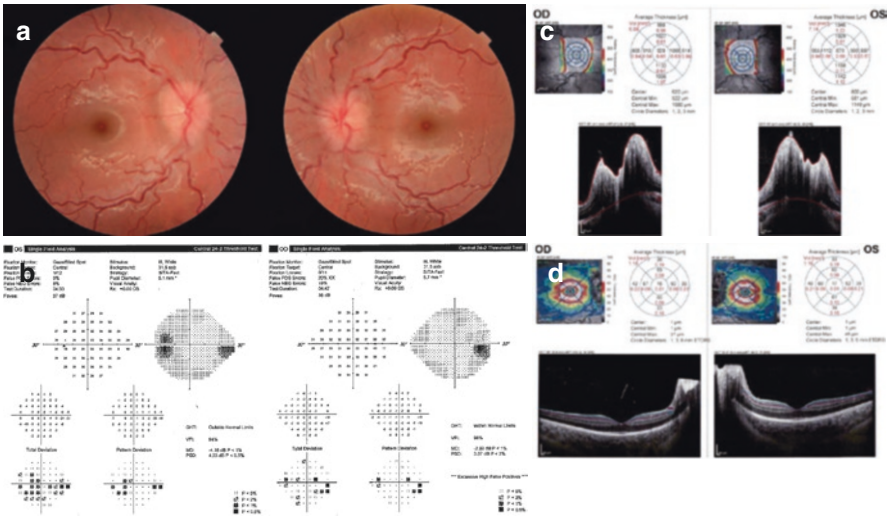

Fig. 9.2 A representative case of a thin, Caucasian 10-year-old girl who presented to the Emergency Department due to worsening headaches. She started to develop headaches, neck pain, and diplopia that progressively worsened over a 3-week period. She had an MRI brain without contrast and MRV that was notable for a partially empty sella, protrusion of the optic nerve heads into the globes, and focal narrowing of the dominant right transverse venous sinus. She had a lumbar puncture performed and her opening pressure was 25 cm H_2O with bland constituents. She was started on acetazolamide in the setting of a borderline opening pressure with other clear signs of increased intracranial pressure. Given the history of headaches, neck pain, and diplopia in the setting of her nontoxic appearance and the fact that she did not fit the typical body habitus for IIH, it was thought that she likely had viral meningitis leading to increased intracranial pressure. On her initial exam, she had normal afferent visual function and bilateral Frisen grade 3 papilledema. (**a**) Her automated perimetry demonstrated an enlarged blind spot bilaterally. (**b**) There is poor reliability of the right eye due to high false positives and this probably served to blunt the presentation of the enlarged blind spot in that eye. The left eye also has a hint of an early nasal step. The optic nerve head volume demonstrates marked elevation in both eyes. (**c**) The ganglion cell layer for both eyes shows no evidence of atrophy in either eye. (**d**) She was started on acetazolamide and had profuse vomiting after each dose. She was transitioned to topiramate and gradually increased to a goal dose of 50 mg twice daily which is approximately 1.5 mg/kg/day). Three months later fundus photography demonstrates resolution of papilledema. (**e**) Her visual fields had normalized with only a hint of an enlarged blind spot in the left eye (**f**). OCT RNFL (**g**) was now performed given the resolution of the edema and her OCT ganglion cell layer (**h**) remained within normal limits though slightly lower than it had been on presentation

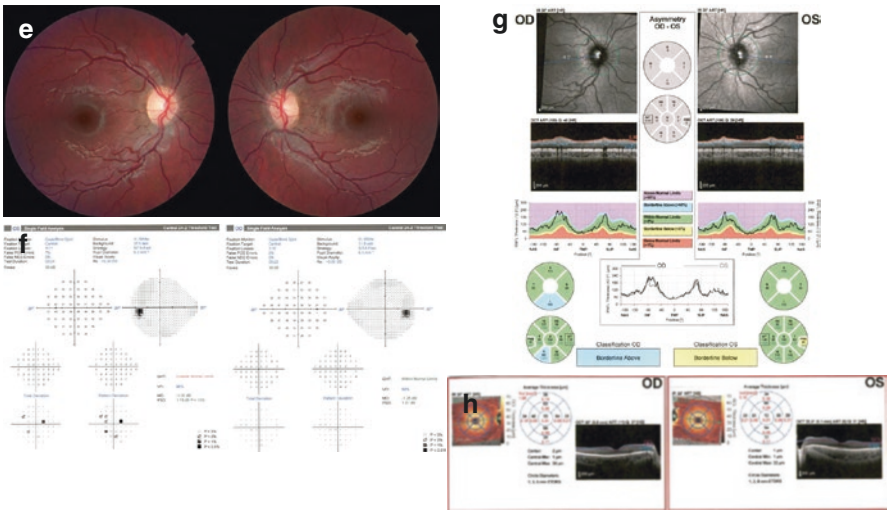

Fig. 9.2 (continued)

pediatric neuro-ophthalmology. Timely distinction between papilledema and pseudopapilledema can be clinically challenging even for the most experienced clinicians.

Optic nerve head drusen are present in 1–2.4% of the population, and their presence is often unknown to the patient [26–28]. Several different methods may be employed to identify optic nerve head drusen, including fundus autofluorescence, extended depth of imaging optical coherence tomography (OCT), B-scan ultrasound, and fluorescein angiography. Though it remains unclear which is the most reliable in children, each has advantages and disadvantages that make their use suitable or impossible in different clinical circumstances [29–31]. Further detail on the approach to diagnosing optic disc drusen is beyond the scope of this chapter. Once a diagnosis of optic disc drusen is made, it is critical for the clinician to remember that this does not preclude the presence of increased ICP. This conundrum places added emphasis on the importance of collecting a complete and thorough history with careful interpretation to accurately identify patients with elevated ICP.

9.4.2 Diagnostic Criteria

The diagnostic criteria for primary and secondary pseudotumor cerebri syndrome have evolved as new diagnostic tools and clear data surrounding their utility become available. Walter Dandy was the first to report a cohort of patients with increased ICP in the absence of brain tumor in 1937 [32]. He described 22 patients with symptomology consistent with increased ICP, normal neurologic examination with the exception of sixth nerve paresis, bland cerebrospinal fluid profiles, and normal

ventriculograms [32]. These key features serve as the foundation for the Dandy criteria, later modified by J. Lawton Smith in 1985 [33]. These criteria were further refined in designing the Idiopathic Intracranial Hypertension Treatment Trial (IIHTT) to include specific threshold opening pressure values on lumbar puncture of >25 cm H_2O or between 20 and 25 cm H_2O with other evidence of increased ICP) [34].

Friedman et al. published the most recent diagnostic criteria for pseudotumor cerebri syndrome in 2013 that included specifications for pediatric patients [1] The critical determinant in these criteria is the presence or absence of papilledema. "Definite pseudotumor cerebri" is applied to patients with papilledema, a normal neurologic exam (except for cranial nerve 6 paresis), normal neuroimaging, bland cerebrospinal fluid composition, and an elevated opening pressure. On neuroimaging, evidence of hydrocephalus, mass or structural lesion, or enhancement if contrast was used should be absent. The authors proposed that all patients should undergo neuroimaging with contrast, and MRV should be performed in atypical presentations, such as in male or nonobese patients. For patients who cannot undergo MRI (e.g., those with pacemakers or other MRI-incompatible implanted hardware), a contrast-enhanced CT is acceptable [1].

A diagnosis of pseudotumor cerebri can be made if patients without papilledema when all other diagnostic criteria are met and there is either evidence of sixth nerve paresis or 3/4 signs of increased ICP are evident on MRI. Signs of increased ICP on MRI include flattening of the posterior globes, empty or partially empty sella, distension of the optic nerve sheaths, or evidence of transverse venous sinus stenosis [1]. The inclusion of MRI findings as supportive evidence for pseudotumor cerebri syndrome is based on multiple different adult and pediatric studies. Kohli et al. performed a retrospective review of 119 patients with at least probable pseudotumor cerebri syndrome, no papilledema but increased ICP, and controls. They found that the presence of three or more MRI findings carried 62% sensitivity and 95% specificity [35]. Comparing MRI findings between adults and children with IIH, Hartmann et al. found that while children have similar findings, prepubertal children were less likely to exhibit all four findings [36]. Gilbert et al. performed a retrospective analysis of 38 patients with and 28 patients without IIH to evaluate MRI findings and found that patients with IIH were more likely to exhibit all 4 imaging features. They additionally reported that an optic nerve sheath diameter of ≥5.2 mm carried 87% sensitivity and 67% specificity for the diagnosis of IIH [37].

At our institution, we limit the use of gadolinium contrast in children given emerging evidence of long-lasting deposition in the brain and the uncertainty concerning its potential impact [38]. Our neuroimaging protocol for suspected pseudotumor cerebri includes MRI brain and orbits without contrast and MRV head. Contrast can be administered when there is concern for an autoimmune, oncologic, or infectious etiology, and at our institution is done at the radiologist's discretion unless requested [37]. The importance of including MRV in children is underscored by Hollander et al. who performed a retrospective review of 360 patients with IIH or papilledema from another cause and discovered that 10/72 (14%) children imaged by MRV 10 had occult dural venous sinus thromboses. Notably, 6/10 were asymptomatic [39].

The threshold for what is considered an elevated opening pressure on lumbar puncture depends on whether sedation is used and its weight. A cutoff of ≥28 cm H_2O is applied in children who are sedated and/or obese and ≥25 cm H_2O in non-sedated, nonobese children [1]. Applying these criteria to a retrospective cohort spanning 4 years, Gerstl et al. found that only 8/12 patients diagnosed with IIH met the criteria for opening pressure and 4/12 met the criteria for definite IIH [40]. Masri et al. evaluated a cohort of IIH patients aged 7 months to 12 years and found that 5/19 had opening pressures lower than 25 cm H_2O [41]. In a cross-sectional study at Boston Children's Hospital who had a lumbar puncture to evaluate for IIH, we found that only 105/374 (28%) patients met the diagnostic criteria when these opening pressure cutoffs were used [42]. While the guidelines provide a numerical basis for diagnosis, it is important to remember that the utility of any test depends on its accuracy and reliability. Lumbar puncture and measurement of opening pressure can be challenging and may yield spurious results even when seemingly performed correctly by an experienced provider. Clinician expertise, patient positioning, sedation, and number of attempts can all influence the results. Thus, clinical presentation and clinician judgment take precedence in the diagnosis of pseudotumor cerebri.

9.5 Treatment

Treatment of pediatric pseudotumor cerebri syndrome depends on the clinical context. The approach to treatment is multifaceted, with both medical and also surgical interventions available. The initial management is focused on lowering ICP on an appropriate timescale and to a level that will minimize the risk of visual sequelae. Contrary to popular belief, the volume of fluid removed during the diagnostic lumbar puncture as well as the closing pressure measurement do not influence the time to resolution of symptoms or papilledema [43].

Oral acetazolamide is the first-line therapy in non-fulminant case. In the pediatric population, acetazolamide is dosed based on patient weight—typically 10–25 mg/kg divided 2–3 times daily. There is no dedicated study demonstrating the effectiveness of acetazolamide treatment in pediatric PTCS. Practice is guided by data from the Idiopathic Intracranial Hypertension Treatment Trial, which compared oral acetazolamide therapy with weight reduction measures alone in mildly affected adults. Acetazolamide improved visual outcomes and reduced papilledema, though headache was not as responsive to the therapy [44]. Acetazolamide is a carbonic anhydrase inhibitor and is presumed to mediate its effect by reducing CSF production.

While acetazolamide dosing has been dosed up to 100 mg/kg/day, with maximum doses of 2 g per day in children and 4 g per day in adolescents, we have found these ranges to be infeasible because of side effects including lethargy, decreased appetite, paresthesias, gastrointestinal upset, and metabolic acidosis [15]. Although the IIHTT found adverse effects of high acetazolamide doses to be uncommon and did not recommend regular blood testing, in our practice, we have found that pediatric patients tend to be more sensitive to adverse effects of high acetazolamide

dosing. We recommend electrolyte testing to evaluate for metabolic acidosis within 2–6 weeks after starting acetazolamide. Depending on symptomology and the degree of acidosis, we replete with oral bicarbonate (usually sodium citrate) with a goal of keeping the bicarbonate level ≥18 mEq/L.

Acetazolamide is widely considered first-line therapy in both adult and pediatric pseudotumor cerebri, but topiramate or furosemide are also used. Topiramate functions as an anticonvulsant by blocking sodium channels, enhancing the activity of GABA (A) and antagonizing certain glutamate receptors, but it also has weak carbonic anhydrase inhibitory activity. Topirimate may be administered a pill or a "sprinkle" for children who are too young to swallow pills. Dosing usually starts between 15 and 25 mg daily and should be up-titrated to 2–4 mg/kg/day divided twice daily to a maximum of 200 mg/day. Topiramate is teratogenic and should be avoided in female patients of childbearing age. Only one open-label study has compared the efficacy of topiramate and acetazolamide and this was an open-label study that found them both efficacious [45]. Topiramate should not be used in combination with acetazolamide due to a theoretical increased risk of kidney stones [46]. Furosemide can also be used as an alternative in patients with intolerance to acetazolamide and topiramate, but its efficacy is also poorly understood [47]. High-dose corticosteroids have been in cases with concern for imminent vision loss, though not for regular or long-term use [48].

Once the ICP is felt to be normalized, as evidenced by resolution of symptoms and papilledema, the question becomes how long to maintain patients on therapy before initiating a medication taper. Unfortunately, the same challenges in diagnosing pediatric patients, such as inability to perform a Snellen visual acuity, to sit for OCT testing or participate reliably with automated perimetry, apply to their follow-up care and limit the data available to guide clinical decision-making. Tovia et al. evaluated 60 pediatric patients with pseudotumor cerebri initially successfully treated (average duration 12 months) with acetazolamide and found that 26% of them suffered a relapse on discontinuation of medication [49]. There remains a great need to define optimal therapeutic practices in pseudotumor cerebri (both primary and secondary).

Clinical considerations that typically guide the initiation of a medical taper are largely focused on whether the driving factor(s) has been adequately addressed and the status of optic nerve health and function. In pubertal/postpubertal IIH, weight loss of 6–10% of body weight is a standard benchmark in adults. In secondary pseudotumor cerebri, discontinuation of a suspected inciting medication or addressing an underlying condition such as anemia or dural venous sinus thrombosis are requisite steps prior to initiating a taper. The clinician may be more conservative in initiating a taper in cases where optic atrophy reaches a significant level or further potential visual morbidity with a relapse would be considered particularly damaging. Orme et al. found that 2/52 (4%) patients diagnosed with pseudotumor cerebri secondary to doxycycline had disease recurrence after cessation of therapy, though the timing and circumstances surrounding these recurrences were not reported. The disease course was significantly shorter (18.3 weeks vs. 62.9 weeks) in the

secondary pseudotumor cerebri vs. the IIH subgroup [21]. Liu et al. reported that the time to resolution of papilledema in cerebral venous sinus thrombosis is approximately 6 months [22]. Thus, the duration of anticipated treatment for pseudotumor cerebri depends on the kinetics of resolution of the underlying factor.

Surgical intervention to reduce ICP is considered in patients who either fail medical therapy or present with fulminant signs and cannot risk waiting for medical therapy to take effect. Surgical interventions include optic nerve sheath fenestration, CSF diversion procedures, and venous sinus stenting. Optic nerve sheath fenestration provides a novel pathway for CSF to egress from the subarachnoid space, which extends along the optic nerves, and thus lessens the pressure burden on the optic nerves [50]. This procedure carries the risk of severe vision loss and is typically performed unilaterally in the worse-seeing eye by an experienced oculoplastics-trained surgeon or neurosurgeon.

CSF diversion procedures for elevated ICP (including ventriculoperitoneal and lumboperitoneal shunting) have been used to address refractory or emergent intracranial hypertension for many decades. Implantation of requisite hardware is not without risk; shunts can subsequently become obstructed, migrate attract infection, or otherwise fail [51]. Brune et al. evaluated complications of ventriculoperitoneal shunts initially placed for IIH at their institution and found 6/32 (18.7%) of shunts failed over 10.75 years follow-up [52]. The authors noted 38 Emergency Department presentations across 14 patients because of potential shunt failures subsequently determined to be functional [52]. In pediatric patients, implanted hardware will inherently remain in place for longer periods of time, potentially amplifying the lifetime risk of failure and other complications. Furthermore, signs and symptoms of potential shunt failure may be less apparent in young children, possibly leading to even more hospital visits, testing and anxiety for the patient and family [52]. Therefore, shunt placement in the pediatric population requires special considerations with generally a higher threshold for placement.

One alternative to permanent CSF diversion is placement of a temporary lumbar drain. This provides protection against ongoing pressure-induced vision loss through an immediate lowering of ICP while acetazolamide can be up-titrated. High-dose glucocorticoids are often used as adjuvant therapy during this process as well [53]. Ploof et al. examined 9 patients with fulminant pediatric IIH who received either a temporary lumbar drain [4], a temporary lumbar drain followed by a shunt [2], or only a shunt alone [3, 54]. All 9 were eventually tapered off medication with resolution of papilledema, though 6/9 had mild residual visual field defects. Less favorable outcomes have also been reported with placement of lumbar drains [53]. The potential role of lumbar drains as a temporizing measure in select cases of fulminant IIH is promising, but requires further study to determine the risk-benefit favorability in comparison to permanent CSF diversion surgery [54].

Venous sinus stenting is a recently developed treatment modality for primarily adult patients with pseudotumor cerebri that have failed medical therapy. The potential utility of this novel approach is under active investigation in both adult and pediatric populations. The approach is predicated on the idea that venous sinus

stenosis (although generally felt to be secondary to elevated ICP) contributes to elevated ICP by obstructing venous outflow in IIH [55]. Dwyer et al. noted that 76/145 (52%) patients with suspected IIH had evidence of obstruction on the dominant side of their venous systems [56]. Carter et al. described 12 reported pediatric patients undergoing venous sinus stenting for medically refractory IIH and noted that larger decreases in the pressure gradient across the shunted region of stenosis correlated with symptom resolution. Requisite revision of stents has been reported to be 13% at 1 year after insertion, compared to 55% of shunts in that same time frame [57]. Placement of the stent requires cerebral angiography which carries an inherent risk for morbidity and mortality. Anti-platelet therapy for 6 months if required after stent placement, carrying additional risk and/or potentially complicating the feasibility of a shunting procedure if needed [55]. As such, venous stenting is more appropriately considered in patients with more severe diseases.

Schwarz et al. reported 8 patients (4 male and 4 female, aged 4–18) with IIH who were refractory to medical management, intolerant to medications or fulminant at presentation, and underwent venous sinus stenting [58]. All patients had stenosis of the venous sinus system and 7/9 had improvement in symptoms with resolution of papilledema and normalization of CSF pressure. Two patients required a repeat procedure, one of whom responded well and one who went on to require multiple other surgical interventions with poor responses [58]. As with lumbar drains, further dedicated studies are needed to identify the ideal clinical scenarios in which venous stenting may provide patients with optimal benefit in light of the risks inherent to this procedure and its subsequent management.

9.6 Monitoring

Effectiveness of medical or surgical treatment of pseudotumor cerebri must be closely monitored, typically with focus on the optic nerve appearance and visual function. The quality and reliability of these data are inherently lower in pediatric patients, depending on the age and developmental status of the child. Effectiveness of treatment is determined by monitoring for decrease in afferent visual function on visual acuity, color vision, and perimetry testing as well as reduction in papilledema both subjectively on fundus exam as well as quantitatively using ancillary testing. For children who are unable to perform automated perimetry, we attempt kinetic perimetry to define their peripheral vision. OCT has emerged as a very helpful tool in this regard by providing objective measures of optic nerve head anatomy (i.e., the degree of swelling and/or atrophy) as measured through the peripapillary retinal nerve fiber layer (RNFL), optic nerve head volume (ONHV), and macular ganglion cell layer (GCL) or complex (GCC, which summates ganglion cell layer and inner plexiform layer) [25]. Importantly, the increased thickness of the RNFL is not specific to increased ICP and can be seen in other forms of optic disc edema such as optic neuritis which more commonly presents with optic disc edema in children [25, 59].

In the IIHTT, 90% of eyes with papilledema had mean RNFL thickness measurements above the 95th percentile of normal [60]. ICP at 6 months after treatment, mean RNFL thickness decreased more in the acetazolamide group compared to placebo with diet [61]. Similar decreases in both total retinal thickness and optic nerve head volume measurements were also observed [61]. While measurement of RNFL thickness with OCT is often used in neuro-ophthalmologic disease processes, the segmentation algorithm becomes less reliable once the mean RNFL thickness exceeds 200 μm [25]. Thus, whereas RNFL measures mirrored clinically meaningful group differences in the IIHTT, it is not an ideal metric with which to follow patients, particularly if the purpose is to identify treatment response failures. For this reason, we prioritize the use of ONHV as it is less prone to error in the setting of papilledema, though formal evaluation of this remains limited [25, 34, 60–62].

It is important to remember that reductions in retinal nerve fiber layer thickness and optic disc volume may represent the resolution of papilledema, these changes are also seen with the progression toward optic atrophy. Measurement of the macular ganglion cell layer (or ganglion cell complex, which includes the inner plexiform layer) allows for direct assessment of optic atrophy in the setting of a swollen optic nerve. As with the RNFL, atrophy in the form of thinning may not be evident in the acute stage as it typically manifests 6–8 weeks after an axonal insult. Therefore, we recommend performing measurements of the ganglion cell layer or ganglion cell layer complex in addition to formal perimetry (automated or kinetic) at each evaluation. Thinning of the ganglion cell layer is directly representative of optic atrophy and tends to manifest prior to the thinning of the retinal nerve fiber. As with the RNFL however segmentation of the ganglion cell layer/complex may fail in situations where the papilledema is greater than or equal to Frisen grade 3. Failures tend to report artifactual thinning, which was noted in 20% of the study eyes that were enrolled in the IIHTT [25, 60, 63]. Algorithms that may reduce these errors are under investigation [25].

9.7 Outcomes

IIH was initially coined a “benign” condition until the potential for profound vision loss in children became more widely known [64]. This may be at least in part because the same difficulties that arise during examination and diagnosis in children make it more challenging to accrue data on their visual outcomes. One retrospective review at a single tertiary care center of 96 patients demonstrated that there was a higher likelihood of a poor visual outcome in pubertal patients vs. prepubertal or adult patients with IIH [65]. Soiberman et al. evaluated 90 patients <10 years retrospectively and found significant improvement in visual acuity with medical therapy [66]. Using OCT, Gospe et al. evaluated visual and structural outcomes in 31 children with IIH and found that 19% had a permanent visual loss (either visual acuity or visual field) and loss of function correlated with the degree of atrophy [67]. Thus, while the majority of patients with pediatric IIH do well, optic atrophy and permanent vision loss are common.

Data on the visual outcomes of secondary pseudotumor cerebri syndrome in children are limited. Orme et al. found that shunts were placed in 3.8% of both the tetracycline-induced pseudotumor (2/52) and the IIH patients (11/302), while 4/52 (7.7%) of the tetracycline-induced pseudotumor cerebri group underwent optic nerve sheath fenestration compared to 28/302 (9.2%) of the IIH patients [25]. Both groups had a similar rate of afferent pupillary defects (Secondary: 6/52, 12%; IIH: 25/302, 8.3%). The visual outcomes of the tetracycline-induced pseudotumor cerebri group were not described further [21]. In their study of adults and children with cerebral venous sinus thrombosis, Liu et al. noted a mean visual acuity outcome of 20/25, though the range included light perception. Visual field defects were noted in 26/65 (40%) patients at the final visit [22]. Grade ≥ 3 papilledema or progression of papilledema after initiation of treatment were associated with visual field loss at the final follow-up visit [22]. Thus, primary and secondary pseudotumor cerebri syndrome can lead to permanent visual loss in adults and children. Further research characterizing visual outcomes in the pediatric population is greatly needed.

9.8 Conclusion

Primary and secondary pseudotumor cerebri occur in children as well as adults. These diagnoses require a clear and algorithmic approach in their evaluation to identify and address causative factors. It is crucial not to overlook any elements of the work-up, including a detailed patient history, examination, neuroimaging, and lumbar puncture with careful measurement of the opening pressure. Formal diagnostic criteria should be applied in making a diagnosis of primary pseudotumor cerebri syndrome (IIH) et al. [1]. It is important to maintain a high index of suspicion for borderline cases. Prompt recognition and treatment are crucial to prevent permanent vision loss. Interventions include medical therapy, a temporary lumbar drain, or surgical procedures such as csf diversion, optic nerve sheath fenestration, or venous sinus stenting.

Unlike its adult counterpart, pediatric primary pseudotumor cerebri has different risk factors and anthropomorphics depending on age and pubertal status. Prepubertal pseudotumor cerebri is equally common in males and females and there is no association with obesity whereas the anthropomorphics of postpubertal pseudotumor cerebri are more similar to those of adults. Pediatric patients, especially prepuberty, are more likely to present without classic symptoms including headache, visual changes, pulsatile tinnitus, or transient visual obscurations. The difficulty in examination and acquisition of ancillary data make the diagnosis of pseudotumor cerebri more challenging in children. These same limitations hinder the quality and quantity of research in this vulnerable population. Nevertheless, further work in multiple domains of this potentially sight-threatening condition is needed to guide diagnostic and treatment guidelines.

Key Points

1. Pediatric pseudotumor cerebri syndrome can be either primary (idiopathic) or secondary to medications, systemic disease, or venous sinus outflow obstruction.
2. Evaluation of pediatric pseudotumor cerebri syndrome requires a systematic and algorithmic approach including detailed patient history, examination, neuroimaging, and lumbar puncture with measurement of opening pressure.
3. A significant fraction of pediatric patients with pseudotumor cerebri will suffer permanent visual loss and/or optic atrophy, which can be prevented or minimized with timely and appropriate medical and/or surgical intervention.

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