

MAJOR REVIEW

Pediatric Idiopathic Intracranial Hypertension

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Abstract. Our understanding of pediatric idiopathic intracranial hypertension has been refined since Dr. Simmons Lessell's review in 1992. The use of rigorous methodologies and standard definitions in recent studies has demonstrated distinct demographic trends. Specifically, the incidence of idiopathic intracranial hypertension seems to be increasing among adolescent children, and among older children its clinical picture is similar to that of adult idiopathic intracranial hypertension (female and obese). Within younger age groups there are more boys and nonobese children who may develop idiopathic intracranial hypertension. The pathogenesis of the disease has yet to be elucidated. Idiopathic intracranial hypertension among young children has been associated with several new etiologies, including recombinant growth hormone and all-trans-retinoic acid. More modern neuroimaging techniques such as MRI and MRI-venograms are being used to exclude intracranial processes. Although most cases of pediatric idiopathic intracranial hypertension improve with medical treatment, those who have had visual progression despite medical treatment have undergone optic nerve sheath fenestration and lumboperitoneal shunting. Because idiopathic intracranial hypertension in young children appears to be a different disorder than in adolescents and adults, separate diagnostic criteria for younger children are warranted. We propose new criteria for pediatric idiopathic intracranial hypertension in which children should have signs or symptoms consistent with elevated intracranial pressure, be prepubertal, have normal sensorium, can have reversible cranial nerve palsies, and have an opening cerebrospinal fluid pressure greater than 180 mm H₂O if less than age 8 and papilledema is present, but greater than 250 mm H₂O if age 8 or above or less than 8 without papilledema. (*Surv Ophthalmol* 52:597–617, 2007. © 2007 Elsevier Inc. All rights reserved.)

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I. Introduction

Idiopathic intracranial hypertension (IIH) is a condition defined by elevated intracranial pressure but no clinical, laboratory, or radiographic evidence of responsible infection, vascular abnormality, space occupying lesion, or hydrocephalus.⁵⁷ Simmons Lessell's review of IIH in children,¹⁰⁷ published in *Survey of Ophthalmology* in 1992, provided a general overview, protocol for diagnosis, and review of conditions associated with this disorder in the

pediatric age group. Since then, however, further delineation of the demographics of children with IIH, recognition of additional cases with reversible cranial nerve palsies, new etiologies and associations, and updated management strategies have been described in the literature. In light of these developments, we consider it important to provide an updated review. We plan to focus specifically on advances since 1992, with the goal of supplementing ophthalmologists' current fund of knowledge

regarding pediatric IIH and its diagnosis and management. Finally, our review has prompted us to propose criteria for the diagnosis of pediatric IIH.

A. NOSOLOGY

Because IIH is the preferred term, a brief nosological discussion is warranted. A multitude of terms, including “serous meningitis,” “otitic hydrocephalus,” “angioneurotic hydrocephalus,” “meningeal hypertension,” “hypertensive meningeal hydrops,” “pseudotumor cerebri,” and “benign intracranial hypertension” have been used to describe the syndrome.⁹ Initially, “pseudotumor cerebri” was preferred because the patient’s presenting symptoms were consistent with those of a cerebral mass. Later, because the mechanism of the disease seemed to rely on increased intracranial pressure, “intracranial hypertension” was favored in the name. Although initially favored, the adjective “benign” was deemed unsuitable because permanent vision loss, a known complication, could hardly be associated with a benign disease process. For these reasons, idiopathic intracranial hypertension (IIH) became the most favored term.^{146,158} We should point out, however, that we do not believe that the disease is truly idiopathic. Although the exact mechanism remains elusive, there are several hypotheses regarding the possible etiologies. As a result, we shall use prudently the name “idiopathic intracranial hypertension,” recognizing that in years to come, this term too may become outdated.

B. DIAGNOSTIC CRITERIA

IIH’s definition has evolved, and currently the modified Dandy criteria must be met as a prerequisite for adult diagnosis.^{168,191} With advances in neuroimaging and recognition of secondary causes, the criteria have been updated to include: 1) general signs and symptoms of generalized ICP or papilledema, 2) elevated cerebrospinal fluid pressure (greater than 250 mm H₂O), measured in a lateral decubitus position, with normal composition, 3) no evidence of hydrocephalus, mass, structural, or vascular lesion on MRI or contrast-enhanced CT for typical patients, and MRI and MR venography for all others, and 4) no other identified cause of intracranial hypertension.⁵⁷ However, no specific diagnostic criteria for pediatric IIH currently exist. We believe that as our understanding of pediatric IIH and its demographics and clinical manifestations has evolved, the current criteria warrant revision as they may inappropriately exclude some cases and inappropriately include others.

C. PATHOGENESIS

The pathogenesis of IIH is still not completely understood. Although brain edema, increased cerebral blood volume, and increased cerebrospinal fluid secretion have been postulated to be associated with the condition,^{82,170} most attention has been focused on increased venous sinus pressure and decreased cerebrospinal fluid absorption. Decreased absorption at the level of the arachnoid villi has been demonstrated by radioisotope cisternography, although it is unclear whether it is secondary to compression of the arachnoid villi or by elevated intracranial pressure itself.¹¹³ Karahalios et al have suggested that elevated intracranial venous pressure is a universal mechanism of all IIH, both adult and pediatric.⁸⁶ Elevated venous pressure may increase resistance to CSF absorption, subsequently causing the cerebrospinal pressure to increase as well. Others have refuted this theory by suggesting that because venous sinus stenoses reverse with correction of elevated pressure, elevated venous pressure could be an effect, rather than a cause, of intracranial pressure.^{11,73,124} In another study, the authors argued that reduced venous sinus pulsatility may be a marker for IIH secondarily to raised venous pressure.¹² Unfortunately most of the studies regarding pathogenesis of IIH have studied adults; similar studies in children have not been done.

D. HEREDITARY BASIS

A hereditary basis has been suggested for IIH in several reports.^{60,61,87,160} The cases include homozygous female twins,⁶⁰ heterozygous female twins,⁶¹ siblings,⁸⁷ mother–daughter pairs,⁸⁷ mother–son pairs,¹⁶⁰ and cousins.⁸⁷ Unfortunately, genetic linkage analyses are lacking, and the genetic mechanism by which the disorder might be transmitted is far from clear.

II. Demographics and Epidemiology

Idiopathic intracranial hypertension can occur at any age in childhood, although IIH in infants is uncommon¹²⁵ and in neonates is exceedingly rare.

The incidence of idiopathic intracranial hypertension in the overall population is 1 out of 100,000.⁶⁴ However, recent studies have elucidated demographic trends in pediatric IIH.

A. PUBERTAL VS. PREPUBERTAL

Previously, IIH was thought to occur with equal incidence in all age groups.^{7,107} It now appears that there is an increasing incidence of IIH among adolescents (12–15 yrs) as compared to young

children (2–12 years).⁶⁴ This might reflect the growing trend of obesity in adolescence or a related greater awareness among medical professionals of the association between IIH and obesity. One study reports that as many as 60% of children who develop the disorder are over 10 years of age.⁷

There is also now a growing sentiment that IIH is different in younger children than in older ones,³⁶ with no sex predilection or tendency for obesity in younger patients (see subsequent discussion), and that the developmental milestone which separates the younger and older groups is the onset of puberty.²⁹ One recent report also suggested that pubertal patients had a less favorable visual outcome than prepubertal, teenage, and adult patients.¹⁷⁵ However, both sets of authors used age to define prepubertal and pubertal status: Cinciripini et al included age 11 years and younger as prepubertal.²⁹ Similarly, Stiebel-Kalish et al¹⁷⁵ defined males 13–15 years of age and females 11–15 years of age as pubertal in one combined age- and sex-specific criteria, and used ages 9–16 years, boy or girl, in another set of age-specific but sex non-specific criteria. Although we agree that onset of puberty is an important milestone in IIH, age-specific criteria to define puberty are unreliable. Rather, because age of onset of puberty varies from person to person, standard criteria based on secondary sexual characteristics^{120,121} should be used.

B. OBESE VS. NONOBESE

In adults, there is a well-established association between obesity and IIH.¹⁵⁵ In contrast, according to one meta-analysis of children with IIH and one retrospective review, only 30% of children with IIH were overweight.^{7,164} Both sets of authors suggested that, at best, there was a weak association between pediatric IIH and obesity.^{7,164} However, these studies did not incorporate standard definitions of pediatric obesity, age subgroups were not examined, and complete ascertainment of data pertaining to obesity was not always achieved.

More useful information has been provided by Balcer et al,⁸ who used rigorous methodologies and standard definitions of obesity in children with IIH, and trends with age were examined. The records of 40 patients were studied; all met the clinical criteria for IIH and had height and weight recorded at presentation. Subjects were classified as obese if they weighed more than 120% of ideal body weight. The authors found that 43% of patients aged 3 to 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 criteria for obesity (p = 0.01). With the use of statistical methods, this study

established that older children with IIH were more likely to be obese than younger children.⁸

C. MALE VS. FEMALE

Recent studies have shown that in younger children as many as half are boys, but in the older age group, the vast majority of patients are girls.⁷ In the study by Balcer et al, 50% of patients aged 3 to 11 years were female, whereas 88% of those in the 12- to 14-year age group and 100% of those in the 15- to 17- year age group were female. Previously, it was thought that there was no sex predilection in IIH among children.¹⁰⁷ In adulthood, patients are typically women of child-bearing age.^{42,146}

These recent findings that associate obesity and female sex with IIH in older children suggest that in most teenagers, risk factors for developing IIH might be similar to those in adults. Younger children with IIH are less likely to be obese or female, and it is possible that IIH in this younger age group has a different mechanism. Much has yet to be learned about their differing risk factor profile. Larger collaborative studies need to examine the potential role of neuroendocrine and other factors in determining the relation between age, pubertal status, and obesity in the pediatric IIH population. In addition, in the future, definitions of puberty based on secondary sexual characteristics (i.e., Tanner staging^{120,121}) need to be used, rather than those based on age.

III. Clinical Considerations

A. PRESENTING SYMPTOMS

The course of pediatric IIH varies, and a child may present hours to several years after symptoms begin. While headache, nausea, and vomiting are known classic symptoms, patients may complain of blurry vision, diplopia, and stiff neck as well.^{7,142} Other reported symptoms include increasing head size, photophobia, anorexia, retro-orbital pain, lightheadedness, myalgia, head tilt,^{7,142} as well as preferring a knee-chest position.¹⁷⁶ Patients with IIH have normal levels of consciousness and functioning, in contrast to some children with intracranial mass lesions.¹⁷⁰

Until recently, cranial nerve VI palsies were the only accepted neurological abnormalities permitted in diagnosing IIH. Documented in only 12% of adults,¹⁹² sixth nerve palsies continue to be more common among children with IIH, occurring in 9–48% of this population.^{7,92,142} Additionally, palsies of cranial nerves III,^{92,202} IV,^{92,142,171} VII,^{7,21,142} IX,²⁰² and XII²⁰² have also been noted in children. In the series of Phillips et al,¹⁴² children younger

than 11 years old were more likely to have cranial nerve deficits (59%) compared with older children (39%). The reason for the indirect relationship with age is uncertain. Comitant esotropia worse at distance but without obvious abduction defects (“divergence paresis”) may also be seen. Reversal of the cranial nerve palsy with lowering of the intracranial pressure is required to associate the palsy with IIH. Additionally, other ocular motility disorders such as internuclear ophthalmoplegia (INO),⁵⁶ ophthalmoplegia,⁵⁶ and nystagmus²⁰² have been reported infrequently in children; most often IIH is considered as a cause of these abnormalities only after all other related diagnoses are ruled out. While the mechanism causing these abnormalities is still poorly understood, likely there is some element of nerve or brainstem traction. For instance, it is possible that in cranial nerve VI palsies, increased intracranial pressure can cause inferior displacement of the pons, with traction on the abducens nerve.^{1,101}

Asymptomatic idiopathic intracranial hypertension, which is diagnosed when papilledema is incidentally noticed during a routine physical examination, has become a more well-recognized entity in children.^{36,82,92,196,199,202} This type of presentation is more common in younger age groups. These children have no headache or visual complaints. It is unclear why this occurs; one plausible explanation is that preschool and young school age children often undergo routine eye exams. Except for headache management, these children often receive the same treatment as those with symptoms. Furthermore, the incidence of asymptomatic IIH raises questions regarding the incidence of undetected cases.

B. HEADACHE

Headache is the single most common complaint among children with idiopathic intracranial hypertension, and has been documented in 62–91% of cases.^{7,109,142} Unfortunately, “headaches” are a frequent, vague complaint among most children, including those that are healthy. The distinction is not only complicated by the fact that children are not able to articulate their symptoms effectively, but also by the similar quality of migraine and IIH headaches. Although IIH headaches have been described as being characteristically frontal, severe, pulsatile, and worse on lying down,¹⁷⁰ most suggest that they are similar to migrainous headaches except that IIH headaches tend to be continuous, whereas migrainous headaches are generally more severe and intermittent.¹⁷⁰ Furthermore, studies show that in many cases, differentiating between

IIH and migraine headaches may be difficult because of the fact that IIH may be superimposed upon a primary migraine headache disorder.^{74,122}

Of note, there are also reports of IIH in the absence of headache,^{92,158} either because the child is too young to articulate symptoms¹⁰⁷ or because headaches are completely absent.¹⁹⁶ The reason for lack of headache despite increased cerebrospinal pressure is not known. It has been suggested that as in adults, those children with IIH but no headaches have more neurological signs and vision loss at presentation, and tend to have poorer long-term outcomes.¹⁰⁹ Thus, it is possible that headaches may be a warning sign before vision loss occurs,¹⁰⁹ and aggressive reduction of intracranial pressure and treatment of papilledema is critical.

C. PAPILLEDEMA

Papilledema, ranging from mild blurring of the disk margins to gross disk swelling with hemorrhages and peripapillary exudates, has generally been regarded as a hallmark physical finding of IIH. Most often the disc edema is bilateral, although it can be asymmetric or unilateral as well. Children’s papilledema often resolves after 3 to 6 months of medical treatment, although in some it can last for several more months and lead to optic atrophy. In our experience the severity of papilledema, particularly if pallor and cotton-wool spots are present, is positively correlated with the risk of visual loss.

Clinicians should be careful to differentiate papilledema from pseudopapilledema,¹⁷⁰ defined as an abnormal disk that appears swollen but burying of the vessels by the nerve fiber layer, peripapillary hemorrhages, cotton-wool spots, and exudates are absent.⁷⁷ Most of the cases of pseudopapilledema are due to optic nerve head drusen and congenitally abnormal disks (due to crowding, for example).

As there are children who lack headaches, some patients with IIH, especially infants with open sutures, may not have papilledema.^{92,179,202} Mechanisms accounting for lack of papilledema may include acquired or congenital optic nerve sheath abnormalities and resolution of papilledema in chronic IIH.²⁰⁰ In patients without papilledema, in general there should be no threat of vision loss, and treatment is usually geared towards symptomatic headache management.

D. VISUAL ABNORMALITIES

The incidence and type of visual deficits in children are similar to those in adults. For instance, vision loss in children with IIH is usually mild to moderate and reversible, but in rare instances can

be serious, devastating, and permanent.⁷ At presentation, visual acuity loss is reported in 6–20% of pediatric cases,^{7,29,142,158,202} although visual field loss occurs in up to 91% of cases.^{7,29,92,158} Children can describe various afferent symptoms including transient visual loss, photophobia, and “shimmering lights with colored centers.”¹⁷⁰

When papilledema is present and visual acuity and color vision are both abnormal, optic nerve function should be suspected. However, when color vision is relatively normal in the setting of decreased visual acuity in IIH, retinal abnormalities associated with papilledema, such as retinal folds or macular edema, are the more likely cause.

As in adults, the most common visual field deficits include enlarged blind spots, inferior nasal field loss, arcuate type defects, and constricted fields. Caution should be applied in children with IIH, moderately to severely constricted visual fields, and only mild disk swelling. In such patients, superimposed functional vision loss should be considered.

E. DIFFERENTIATION FROM BRAIN TUMORS

The diagnosis of IIH in children is one of exclusion, as central nervous system neoplasms may similarly present with headaches, nausea, vomiting, and papilledema.^{5,24,126,178} One study reported that in childhood, brain tumors required on average up to three visits to a medical professional before the diagnosis was made.¹²⁶ Unlike children with IIH, those with tumors tend to have headaches that are non-throbbing, deep-aching, and intermittent in nature.¹⁷⁸ A brain tumor might be suspected if the headaches are nocturnal, or present in the early morning or upon arising,¹⁷⁸ or if there has been a significant change in previous headache pattern.⁵⁰ Also, behavior changes, seizures, and focal neurologic deficits are more likely in children with brain neoplasms, as compared to those with IIH.^{5,126}

A contrast-enhanced CT or MRI scan of the brain is usually sufficient to rule out a central nervous system neoplasm when IIH is suspected. Exceptions include subtle infiltrating neoplastic processes such as gliomatosis cerebri, which may escape initial detection by neuroimaging.^{43,95} Leptomeningeal spread of lymphoma, leukemia, and germ cell tumors may also lead to signs and symptoms of elevated intracranial pressure in children with only subtle abnormalities on neuroimaging. The diagnosis may be evident by meningeal enhancement on MRI or cerebrospinal fluid elevation in protein, pleocytosis, or abnormal CSF cytology.²³ In addition, spinal cord tumors may block CSF protein, cause elevated intracranial pressure, and mimic IIH. However, usually there is some clue to the spinal

cord process such as back pain, upper motor neuron signs, or sensory level.

Thus, in addition to neuroimaging, all children with papilledema should have a careful neurological history and examination, by a neurologist preferably, to exclude the possibility of a brain or spinal cord tumor, which might mimic IIH.

IV. Etiologies/Associated Conditions

Although secondary causes for IIH are less commonly identified in adults (most of whom are obese), 53.2–77.7% of pediatric cases have been associated with identifiable conditions,^{164,202} the most common of which include endocrine abnormalities, drugs, and infections. Previously recorded associated causes of idiopathic intracranial hypertension in children include viral infection, hypoparathyroidism, menarche, corticosteroid withdrawal, thyroid treatment, nalidixic acid, tetracyclines, vitamin A toxicity, vitamin A and D deficiencies, head trauma, lupus, acute lymphocytic leukemia, Turner syndrome, galactosemia, galactokinase deficiency, and nitrofurantoin.¹⁰⁷ Although there are no case control studies to date which have identified definitive causes in children, there have been several papers as well as case reports citing conditions that seem to be strongly associated with pediatric IIH. We will elaborate on advances made in understanding previously established etiologies, and will reference new associated conditions (Table 1), the most important of which are synthetic growth hormone and all-trans retinoic acid.

A. ENDOCRINE CONDITIONS

1. Thyroid Replacement

New cases of pediatric idiopathic intracranial hypertension following thyroxine replacement ther-

TABLE 1

Conditions and Medications Recently Associated With IIH in Children

Endocrine
Recombinant (synthetic) growth hormone ^{30,33,53,97,114,117,118,144,148,151,156}
Addison's disease ^{3,32}
Levonorgestrel implants ²
Desmopressin nasal spray ¹³⁷
Other Drugs
Cytarabine ⁵¹
All-trans retinoic acid (ATRA) ^{54,67,116,159,190}
Infections
Acute sinusitis ⁹¹
Varicella ^{99,102}
Other
Miller Fisher Syndrome ¹²⁸

apy in juvenile hypothyroidism have been described.^{20,147} In all the cases, IIH occurred after increasing the dose of thyroxine secondary to persistently elevated thyroid stimulating hormone levels. Thus, it has been hypothesized that rapid correction of hypothyroidism with thyroxine, a major regulator of sodium transport, may result in altered CSF dynamics. Except in one case, the IIH occurred in peripubertal children.¹⁴⁷ Therefore, it is possible that pubertal children may have some endocrine or hormonal factors that predispose them to developing IIH in this setting. Additionally a child with hypothyroidism who developed IIH prior to thyroxine treatment has been reported,¹ but given that the child was female, obese, and pubertal, it cannot be confirmed that hypothyroidism and IIH are associated.

2. Adrenal Corticosteroids

Steroid withdrawal in children with inflammatory bowel disease (IBD) leading to IIH was the subject of two reports. In one study, an adolescent with IBD developed IIH during corticosteroid withdrawal after chronic steroid treatment of his gastrointestinal condition.¹¹² In another, three cases of IIH subsequent to treatment with budesonide, a new-generation potent steroid for Crohn disease in children, were published.¹⁰⁸ All three patients in this report had previously been treated with prednisone, experienced symptom resolution with withdrawal of budesonide, and were successfully treated with prednisone later. However, it is difficult to establish a definite causal relationship between budesonide, a drug with low systemic bioavailability, and IIH in these patients, as confounding risk factors such as hypervitaminosis and iron deficiency anemia were also present in at least one case in this report.

3. Growth Hormone

First reported in 1993, there have been multiple cases of IIH in children treated with recombinant (biosynthetic) human growth hormone (GH).^{30,33,53,97,114,117,118,144,148,151,156} In a large database analysis, the prevalence of IIH in the GH-treated population was approximately one-hundred times greater than in the normal population.¹⁴⁸ An increase in the occurrence of IIH after insulin growth-factor I (IGF-1) therapy has also been reported.¹¹⁷ It appears that risk factors such as obesity, Turner syndrome, chronic renal failure, Prader-Willi syndrome, and delayed puberty can increase the risk of developing IIH in this setting.¹⁵ One study cites 15 patients with renal insufficiency who developed IIH subsequent to treatment with

growth hormone.⁹⁷ All of these patients were concurrently being treated with other medications that have been associated with IIH, but IIH developed shortly after beginning growth hormone therapy.

It has been proposed that growth hormone passes the blood–brain barrier, and acts locally to increase levels of IGF-1, which in turn increases CSF production from the choroid plexus.⁸⁰ Furthermore, it seems as though aggressive GH dosing places a child at a higher risk of developing IIH; thus, starting hormone therapy at the lowest recommended dose, with prudent gradual titration to higher doses if needed, has been advised.³³ Caution must be applied when diagnosing papilledema in a patient with GH deficiency as congenital disk anomalies (hypoplasia or small crowded disks) may be seen in children with hypopituitarism.³¹

When IIH is due to GH treatment, stopping replacement hormone therapy is often sufficient to resolve headaches, papilledema, and elevated CSF pressure. Other causes of intracranial hypertension should still be excluded with neuroimaging and CSF examination. We have used acetazolamide when headaches and vision loss are present. Later restarting the growth hormone at a lower dose typically prevents symptom recurrence.

4. Addison Disease

Although earlier reports suggested a possible association between papilledema and Addison disease (adrenal insufficiency in spite of elevated ACTH levels), only in the last decade have definite associations been made between the two in children.^{3,32} In previous cases, lumbar punctures had not been performed, and patients had multiple other medical conditions and risk factors that may have contributed to development of IIH. The more recently published cases have met diagnostic criteria for both Addison disease and IIH, and glucocorticoid and mineralocorticoid replacement resulted in resolution of symptoms,^{3,32} with one patient requiring additional treatment with acetazolamide.³² Future studies need to further investigate the pathophysiological mechanism leading to IIH; it is possible that elevated levels of serum vasopressin may mediate an increase in brain volume and elevated pressures.

5. Other

Levonorgestrel implants² and desmopressin nasal spray¹³⁷ have been associated in children with IIH, but the mechanism in each case was unclear.

B. INFECTIONS

1. Acute Sinusitis

Although infections such as mastoiditis and chronic sinusitis are known to cause secondary intracranial hypertension via venous sinus thrombosis, there has been a recent report of acute frontal sinusitis resulting in true pediatric IIH that is worth mentioning.⁹¹ As compared to others with chronic sinusitis, this case was not associated with sinus thrombosis. The reason for the development of IIH was unclear.

2. Varicella

Although varicella has previously been implicated as a cause of a variety of neurological conditions in childhood, recent reports have suggested that there might be an association between varicella and idiopathic intracranial hypertension as well.^{99,102} In the first case,¹⁰² a girl presented with headache, nausea, vomiting, and papilledema one week after chicken pox developed. In the next,⁹⁹ an 8-year-old girl presented with idiopathic intracranial hypertension and ileofemoral vein thrombosis 3 weeks after chicken pox, but was found to have a transient elevation of anti-protein S auto-antibodies. There were no definitive intracranial thromboses identified on neuroimaging studies. Neither case was associated with meningitis or encephalitis to suggest viral infection of the nervous system, and both children had normal mental status, making Reye syndrome unlikely. Although the second case may have been confounded by a missed venous thrombosis, the first case is convincing enough to believe that varicella itself may predispose a child to IIH.

3. Measles

An 8-year-old girl with measles was described who developed papilledema with normal MRI and elevated CSF opening pressure.¹⁸² No other cause for the elevated intracranial pressure was found, suggesting the IIH was related to measles. A child with subacute sclerosing panencephalitis, a neurologic condition caused by persistent central nervous system infection by a mutated measles virus, and elevated intracranial pressure without pleocytosis has been reported.¹⁸¹ However, because the child's neurological examination revealed altered mental status and myoclonus, he does not otherwise satisfy the diagnosis of IIH.

C. DRUGS

1. Tetracyclines

Tetracyclines, including related medications such as minocycline, have been linked to

IIH.^{7,26,61,107,145,193} They are commonly prescribed drugs, especially for acne treatment. Previously, there was limited knowledge about risk factors that may predispose children treated with tetracyclines to the development of IIH, but in a recent retrospective study, it was shown that female sex and obesity may predispose some to developing IIH when these medications are used.¹⁴⁵ Additionally, there have been several cases of IIH occurring in twins treated with tetracyclines, and thus, it is possible that genetic susceptibility may also predispose certain individuals to IIH.⁶¹ With cessation of antibiotics, and possibly additional treatment with acetazolamide, symptoms usually resolve.

2. Vitamin A

Vitamin A intoxication may produce signs and symptoms consistent with IIH. In a prospective study on adults, hypervitaminosis (either secondary to increased levels, altered metabolism, or hypersensitivity to vitamin A) was shown to be associated with IIH.^{55,76} Additionally, in a double-blind, randomized, placebo-controlled trial, infants given vitamin A supplementation were more likely to develop bulging fontanelles than those who did not.¹⁰ There have been several reports of infrequent cases of IIH after acne treatment with both tetracyclines (discussed previously) and isotretinoin, a vitamin A derivative.^{55,103,130} Combination therapy seems to increase the risk.

There have also been recent reports on the development of IIH in patients with acute promyelocytic leukemia (APML) treated with all-trans retinoic acid (ATRA), a vitamin A derivative.^{54,67,116,159,190} Several studies have shown that children, especially those under 8, are more sensitive to the effects of ATRA on the central nervous system than adults.^{116,169} Therefore, it has been suggested that lower dose regimens of ATRA should be considered in children to avoid potential side effects such as the development of IIH.³⁵

Although the mechanism of toxicity is still not well understood, recent studies have shown that both serum retinol binding protein (RBP)¹⁶⁵ and levels of vitamin A in the cerebrospinal fluid are elevated in those with IIH, as compared to normal controls. It has been proposed that excess retinol and RBP in the serum are transported to the cerebrospinal fluid where retinol acts as a toxin on the arachnoid granulation resorption mechanism.¹⁹⁴

3. Other Chemotherapy Agents

Although neurotoxicities are common with chemotherapeutic agents, the incidence of idiopathic

intracranial hypertension due to these medications is rare. Treatment with intermediate-dose cytarabine⁵¹ was associated with IIH in an 11-year-old boy with acute myelocytic leukemia. The only other recent report of cytarabine-associated IIH has been in with high-dose therapy in an adult woman with APLM. Cytarabine may disturb the ATPase-dependent choroidal secretion of CSF by depleting phosphorus stores.⁴⁷ There has also been a recent case of IIH thought to be secondary to cyclosporine treatment after a bone marrow transplant in a child.³⁴

D. ANEMIA

Idiopathic intracranial hypertension in children has been associated with several forms of acquired anemia, including iron deficiency,^{187,201} acquired aplastic anemia,^{79,136} and sickle cell disease.⁷⁰ The occurrence of IIH with aplastic anemia is rare, with only two reports of patients in the last 10 years.^{79,136} The mechanism by which anemia causes IIH is unclear, but it has been theorized to be a result of tissue hypoxia leading to increased capillary permeability or abnormalities in hemodynamics leading to increased cerebral blood flow (high-flow state).

E. MALNUTRITION AND RENUTRITION

Idiopathic intracranial hypertension has previously been associated with “catch up” growth following malnutrition.¹⁰⁷ A case report describes the syndrome in a young boy with non-organic failure who subsequently gained 4.6 kg and 1.6 cm in height over 4 weeks. During that time, the boy developed papilledema and headaches.⁴ Both rapid escalations in growth hormone levels as well as rapid brain growth have been suggested to cause an increase in brain edema and intracranial hypertension.

F. MILLER FISHER SYNDROME

Idiopathic intracranial hypertension has been reported as a complication of Miller Fisher syndrome.¹²⁸ This condition, characterized by ophthalmoplegia, ataxia, and areflexia, is a variant of Guillain-Barré syndrome. In the cited study,¹²⁸ two children, ages 2 and 9, presented initially with symptoms of raised intracranial pressure and were later diagnosed with Miller Fisher syndrome. Both children had cranial nerve VI palsies, documented elevated pressure, normal cerebrospinal fluid composition (including normal protein), and normal imaging studies on presentation, and later were diagnosed with Miller Fisher syndrome when they developed loss of deep tendon reflexes and ataxia. One child had anti-GQ1b antiganglioside antibodies

in the serum, and the other had antimyelin antibodies. Both were treated with acetazolamide and intravenous immunoglobulin therapy with improvement of symptoms. Thus, we believe there may be an association between the acute demyelinating condition of the peripheral (and central?) nervous system and pediatric IIH.

G. QUESTIONABLE AND MISTAKEN ASSOCIATIONS

The recent literature is unfortunately still replete with reports of other conditions purported to be causes of IIH. In many of these cases, standard criteria for the diagnosis of IIH have not been satisfied. In others, hypercoagulable states leading to undetected intracranial venous thromboses may have been present, and in some reports, the diagnosis of IIH was likely to be purely coincidental as no plausible explanation for the association between IIH and the described condition could be provided. We review these supposed associations here to emphasize that these conditions have not been convincingly shown to cause IIH.

1. Lyme Disease *no really*

One report suggested that children with Lyme disease, the infection caused by the spirochete *Borrelia burgdorferi*, may later develop IIH.⁸⁵ We present the argument that there is no association between the two syndromes because the standard criteria for the diagnosis of IIH requires the CSF profile to be normal without evidence of meningitis. For instance, in the case of purported IIH in a child with Lyme disease, the MRI showed enhancement of the dura consistent with inflammation, and CSF was significant for 115 cells/mm³, glucose 53 mg/dL, and protein 56 mg/dL, consistent with infection.⁸⁵ Although the child was “diagnosed” with IIH and aseptic meningoencephalopathy, we believe that her headaches, vomiting, and diplopia were a result of increased intracranial pressure secondary to Lyme infection, rather than IIH. In another case reported of a boy with neuroborreliosis claimed to have IIH, the CSF pleocytosis rendered this diagnosis of IIH to be incorrect.⁶⁸

One cautionary note must be applied in this context. At our institution we have seen two patients, one published,¹⁷³ with papilledema due to Lyme meningitis who had little or no pleocytosis on the first lumbar puncture but demonstrated marked pleocytosis on a second lumbar puncture. There should be a high index of suspicion for this type of presentation in endemic areas, and therefore in the future at our institution we might

consider routine serologic Lyme testing in all children with IIH.

2. Renal Transplantation and Impaired Renal Function

Children with impaired renal function may be at higher risk of developing idiopathic intracranial hypertension.¹³¹ Recently, it has also been suggested that those who undergo renal transplant may also be at greater risk post-transplantation.^{18,22,52,62,89,140,166} The development of IIH does not appear to be temporally related to the time of surgery. In one retrospective analysis of children undergoing renal transplant in the United Kingdom over an 11-year period, it was claimed that 4.4% developed IIH post-transplantation.⁵²

However, it must be noted that almost all of the reported patients were treated with chronic immunosuppressive medication, including corticosteroids, and many had other risk factors, including obesity, that could have also increased their risk of developing IIH.²² Additionally, there have been multiple cases of renally compromised children, treated at some point with growth hormone, who developed IIH.⁹⁷ There has also been a case of severe IIH in a boy with chronic renal failure on hemodialysis, who required a kidney transplant, with subsequent resolution of his symptoms.¹³¹

It is still unclear whether some aspect of care after transplantation or impaired renal function post-transplantation place children at higher risks of developing IIH. For example, one author presented a case of pediatric IIH following cyclosporine A treatment in a boy with tubulointerstitial nephritis, but steroids had been withdrawn before the cyclosporine was started.¹⁸

3. Head Trauma

Minor closed head trauma was previously reported in association with pediatric IIH, but the etiology may have been cerebral venous sinus thrombosis.¹⁰⁷ Over the last decade, there has been an additional reported case of head trauma causing IIH in a child,¹³⁸ but neuroimaging demonstrated a thrombosis of the right lateral dural venous sinus. Increased intracranial pressure in head trauma may also be the result of cerebral edema.^{27,188}

4. Prothrombotic States

Hypercoagulable states and dural sinus thromboses have been reported in association with and in some cases are attributed in the mechanism for IIH.^{37,41,177} For instance, it has been proposed that patients with IIH may have genetic thrombotic risk factors that predispose them to microvascular

occlusion in the arachnoid villi.³⁷ In one recent large population study, those with IIH had 31% incidence of antiphospholipid antibodies, 27% had hyperfibrinogenemia, and 27% with other conditions related to thrombosis.¹⁷⁷ Additionally, there are anecdotal reports of the association of anticardiolipin antibodies and IIH,^{105,106} although in one study some of the patients had other risk factors.¹⁰⁵

Lupus and other rheumatologic conditions often associated with a hypercoagulable states have been described as causing IIH.⁶⁶ There have two reported cases of children with lupus, one of whom had leukoencephalopathy,²⁵ and the other who had lateral sinus thrombosis.¹⁸⁹ Similarly, Behcet syndrome is associated with intracranial hypertension secondary to venous thrombosis in 5–50% of cases;⁹⁸ hypercoagulable states were present in both reports of children with Behcet and intracranial hypertension.^{98,195}

According to the standard criteria for IIH, venous thromboses should be excluded. Even when venous thromboses can not be demonstrated with MR-venography or even conventional venography in a patient with elevated intracranial pressure, the presence of a hypercoagulable state suggests that microthromboses might still be a possible cause. Therefore, it is definitely incorrect to diagnose patients with venous thromboses as having IIH, and it is questionable whether patients with hypercoagulable states should be allowed to have that diagnosis as well.

5. Cystic Fibrosis

It has been suggested that cystic fibrosis may be linked with IIH.^{14,115} One author reports an incidence of 7.7% IIH in children with newly diagnosed cystic fibrosis.¹⁴ In the study, three cases of possible IIH secondary to cystic fibrosis are cited; in all cases there were other causes of IIH development including hypovitaminosis, hypervitaminosis, and refeeding syndrome. In another study,¹¹⁵ IIH is described in a slightly older asymptomatic child in whom IIH was diagnosed with cystic fibrosis. While this child had no signs of malnutrition, she did have iron deficiency anemia.

6. Others

There are several other reports in which the association with IIH is unclear because of confounding factors. For instance, in a reported case of a child with IIH possible associated with hemiplegic migraine,¹⁷² the child was taking minocycline for acne. In a case of IIH post-orthotopic heart transplantation,¹⁶³ the child was on immunosuppressive therapy including cyclosporine, azathioprine, and

prednisone. In a bipolar child taking incrementally higher doses of lithium who developed IIH, the patient had several other risk factors including obesity and minocycline treatment for acne.⁷¹ Similarly, in a report of children with cystinosis who developed IIH,³⁸ several were treated with either prednisone, growth hormone, cyclosporine, or thyroid replacement.

In some cases, the diagnoses of IIH have been made in children who do not satisfy the standard criteria. For example, in a case of pediatric IIH attributed to hemophilia A,⁷⁸ the child had an abnormal neurologic exam and had problems concentrating, difficulty with language, and changes in personality.

Several conditions may have occurred coincidentally. For example, there have been cases of pediatric IIH reported to be associated with optic nerve drusen,¹⁵⁴ Goldenhar and Duane syndromes,¹⁸⁵ and bilateral subural hygromas.¹³⁵ In a case report of a 14-year-old girl with IIH, psychotic symptoms were reported.⁴⁰ However, a true association or causation could not be established.

In the cases of IIH purportedly associated with panuveitis¹¹⁹ and Tolosa-Hunt syndrome,¹³⁹ the diagnosis of IIH must be questioned, and an alternative inflammatory or infectious disorder of the CNS would seem to be a more parsimonious explanation.

V. Clinical Evaluation of Children with Suspected IIH

A. HISTORY

Age and sex should be noted. Patients and their parents should be asked whether the child (1) had any recent weight gain, (2) took any medications which predispose to IIH such as tetracycline, chronic steroids which were then tapered, minocycline, or synthetic growth hormone, or (3) has any underlying medical conditions associated with IIH such as Addison disease or systemic lupus erythematosus. Development of secondary sexual characteristics should also be recorded. The child should be asked whether he or she has blurry vision, double vision, transient visual obscurations, headache, nausea or vomiting, neck or back pain, or any other neurological complaints.

B. EXAMINATION

Children with suspected IIH should have careful documentation of visual acuity, color vision, visual fields to confrontation, pupillary examination, ocular motility, dilated ophthalmoscopy, and a neu-

rological examination. Abnormalities in many of these have been alluded to in the previous sections.

C. VISUAL FIELD TESTING

In children who can cooperate, computerized threshold visual field testing should also be performed.^{39,174} Because of its greater sensitivity in IIH, Humphrey 30-2 (Swedish interactive thresholding algorithm [SITA], fast if possible) is preferred over 24-2 perimetry in this setting.⁹⁴ Although some authors have claimed reliable and repeatable SITA visual field testing in children as young as 4 years,¹⁷⁴ in our experience and that of others,⁸⁸ this is rarely accomplished before the age of 8. Partially cooperative children may be tested with Goldmann (kinetic) perimetry. However, a short child may not be able to sit in a chair and be large enough to have the head reach the chin-rest in most automated and kinetic perimetry setups. Having a young short child stand for ten minutes of perimetry is unrealistic.

VI. Optic Nerve Imaging and Related Techniques

Ultrasonography is used frequently in our practice to help distinguish papilledema from pseudopapilledema, in particular when optic disk drusen are suspected. Some authors have suggested optical coherence tomography (OCT), by demonstrating increased retinal nerve fiber layer thickness in papilledema, can be used to make this distinction.¹⁴¹ However, ultrasonography can be performed rapidly, even in young, only mildly cooperative children, whereas OCT requires the patient to hold very still while measurements are acquired.

Other optic nerve imaging techniques, although extremely compelling, are still supplementary to the clinical evaluation and lumbar puncture in the diagnosis and management of patients with IIH. Heidelberg retinal tomography (HRT) can be used to quantify the degree of change in papilledema and measure changes over time in some children with IIH.^{69,186} It has been suggested that tomography measurements correlate with opening pressures in adolescents and adults.⁶⁹ Assessing the diameter of the optic nerve in relation to CSF pressure via orbital ultrasonography may be another useful tool especially in follow-up,¹⁶⁷ and one study suggested ophthalmodynamometry may assist in noninvasive estimation of cerebrospinal fluid pressure through measurement of the central vein pressure.⁸³ However, at this time the role of HRT and other related technologies in the diagnosis and follow-up of children with IIH may be limited to those who are uncooperative with the usual clinical measures, as it

has yet to be demonstrated that they are better or add anything to the clinical examination of visual function, visual field assessment, ophthalmoscopic examination, and lumbar puncture.

VII. Neuroimaging

Normal neuroimaging studies are mandatory before diagnosing pediatric IIH. Computed tomographic (CT) scanning was previously considered adequate to exclude ventriculomegaly or mass lesions. However, because there are conditions such as gliomatosis cerebri and cerebral venous thrombosis that can mimic pediatric IIH and may be missed by CT, it now considered suboptimal, and MRI/MRV of the brain with and without gadolinium are the studies of choice in this setting.¹⁵⁷

A. ADVANCES IN MAGNETIC RESONANCE IMAGING

Magnetic resonance imaging (MRI) is superior to CT scanning because it offers better visualization of intracranial structures, including the venous system, and it avoids the potential risks of radiation exposure. A number of findings on MRI have been demonstrated in pediatric patients with IIH. None of these abnormalities are specific for IIH, but without any other clinical explanation, they often are suggestive of the diagnosis. For instance, in one large study, Brodsky et al showed changes in the distal optic nerves including flattening of the posterior sclera (80% incidence), intraocular enhancement of the prelaminar optic nerve (50%), distension of the perioptic subarachnoid space (45%), and tortuosity of the optic nerves (40%).¹⁶ These findings are best seen with high-resolution, thin-slice MR imaging through the optic nerves.¹⁶ In another study,⁷⁵ a child with headaches, nausea, vertigo, progressive visual loss, and optic atrophy due to IIH had an MRI which showed enlarged perioptic nerve subarachnoid spaces. Additionally, variations in the appearance of the pituitary gland (including empty sella) have been demonstrated in 85–100% of those with IIH.^{180,203} No consistent endocrine abnormalities are found in patients with empty sella, which is thought to result from arachnoid herniation through a defect in the sella diaphragm secondary to chronically elevated intracranial pressure.

B. MR VENOGRAPHY

Before pediatric IIH can be diagnosed, venous sinus thrombosis must also be excluded. The use of MR venography (MRV) as a noninvasive tool for imaging the cerebral venous sinuses and diagnosing

venous sinus thrombosis has become popular over the last decade. Prior to that, conventional MRI and catheter angiography were used to visualize the intracranial vasculature; unfortunately, MRI was limited in accurate visualization of vessels, and angiography was invasive.

Although to date there is limited data in the literature on the use of MRV in younger children with IIH, adolescent and adult patients with the disorder often have distinctive patterns on MRV—narrowing of the transverse (lateral) sinuses, suggesting possible abnormalities in venous blood flow.⁷² It is unclear whether these signal abnormalities are the cause or the consequences of IIH, but the latter is more likely. Previously, it was thought that unrecognized thrombi may be the cause of tapered stenoses and filling defects in transverse sinuses in patients with IIH.⁸⁶ However, the sinus narrowing often resolves with lowering of CSF pressure, implying that increased intracranial pressure caused the collapse of the walls of transverse sinuses.⁹⁶

It should be noted that although there is excellent visualization of most venous structures, there are limitations in the use of MRV. Visualization of transverse sinuses, especially in the setting of chronic thromboses, may be challenging, especially because of wide variations in normal anatomy. One study argued that transverse sinus flow gaps may be normal in up to 30% of people, especially in nondominant (smaller) sinuses.⁶ Other studies have shown evidence for pediatric age-related changes in the venous anatomy such as variations in the dominance of sinuses, involution of the occipital sinuses, and increasing frequency of absent transverse sinuses.^{152,198} Furthermore, MRV may not provide views of sinus continuity, especially in-plane vascular flow, and artifacts may hinder diagnosis.⁶ Thus, flow gaps should be judged with caution, and careful interpretation of MRV is essential.⁶



VIII. Lumbar Puncture

After normal neuroimaging, a spinal tap is mandatory to measure the CSF opening pressure and to exclude meningitis. However, the parameters for spinal fluid opening pressures in younger children may be different than they are in adolescents and adults, and there are more variables. Normal values for CSF opening pressure and cell composition are well established in adults, but determination of normal CSF pressure and composition in children is challenging because of practical reasons and from lack of reliable published data. For example, accurate pressure measurements are often complicated by agitation and crying in young

unsedated patients, and this can transiently elevate readings. Another complicating factor is a possible false elevation of intracranial pressure by hypercarbia during anesthesia.

In addition, several studies in the literature have sought to identify normal opening pressures for both neonates and young children, but studies are often cross referenced and methodologies are inconsistent (Table 2).^{13,45,49,110,127,129,197} After compiling results of previous studies, Fishman suggested that normal levels in a young child can vary between 10 and 100 mm H₂O and will approach adult levels only after the age of 8.⁴⁹ Therefore, using 250 mm H₂O as an upper limit of normal may result in missed cases of IIH. However, other studies have suggested that normal opening pressures in children may be higher than 100 mm H₂O. For instance, Ellis et al.⁴⁵ measured opening pressures in normal children, ages 4 months to 19 years, and calculated a statistical norm of 100 to 280 mm H₂O, using a drop counting method.⁴⁶ However, this technique is not widely used, and measuring opening pressures with a manometer is still preferred.

When pediatric neurology and neurosurgery senior faculty at the Children's Hospital of Philadelphia were polled informally, 180 mm H₂O was felt to be the upper limit for normal opening pressures.

We are currently planning a prospective study of normal opening pressures in children undergoing sedated and unsedated lumbar punctures. The influence of the type of anesthesia and body positioning will be studied.

In the meantime, in the absence of better data, we recommend lumbar punctures 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. We also recommend using the aforementioned upper limit of 180 mm H₂O as the normal opening pressure for children less than 8 years of age with papilledema and using the adult norm of 250 mm H₂O for children ages 8 or above or less than 8 without papilledema.

Moreover, for poorly understood reasons, cell and protein counts can be elevated in neonates. We performed a review of the literature^{45,49,134,143,161} to identify better the ranges of accepted values in a neonate. Mean levels of 8.3 WBC cells/mm³, with an upper limit of 32 cells/mm³ should be allowed,¹⁶¹ and do not preclude a diagnosis of pediatric IIH although as mentioned earlier, neonatal IIH is extremely rare. CSF protein, as well, can be relatively elevated in neonates (up to 150 mg/dl in the first 30 days of life), but will decline to normal levels (15–45 mg/dl) after the first six months of

TABLE 2

Published and Cited Normal CSF Opening Pressure (mm H₂O) in Infants and Children

	Authors, year	Pressure in Infants	Pressure in Children	Comments
Lumbar puncture	Quincke, 1891		40–60	Cited by Fishman ⁴⁹
	Sidbury, 1920	30–70		Cited by Fishman ⁴⁹
	Levinson, 1923		45–95	Cited by Fishman ⁴⁹
	Levinson, 1928	20–70	40–80	Cited by Fishman ⁴⁹
	Munro, 1928 ¹³²	30–80	90–120	Determined from patients treated for cranial and intracranial injury, but symptom free at discharge
	Lups and Haan, 1954		40–100	Cited by Fishman ⁴⁹
Fontanelle or other method	Gerlach et al., 1967	10–14	40–100	Cited by Fishman ⁴⁹
	Kaiser et al., 1986 ⁸⁴	mean 38		Neonates. Standard deviation 19 mm
	Ellis, 1994 ⁴⁵		100–280	Measured in children placed in flexed lateral decubitus position, with drop counting method ⁴⁶
	Welch, 1980 ¹⁹⁷	20–70		Intracranial pressure determined by tilting the infant until the fontanelle is flat and then comparing to the atmospheric pressure at that level.
Hearsay	Gaab et al., 1980		14–122	Cited by Minns et al. ¹²⁹
	Lipton, 1993 ¹¹⁰	50	85	Incorrectly ascribed to Minns et al. ¹²⁹
Textbook or review	Fishman, 1992 ⁴⁹		10–100	Compiled from previous studies
	Menkes, 1995 ¹²⁷	100	110–150	No references given
	Roberts, 2004 ¹⁵⁰	50	85	Ascribed to Lipton ¹¹⁰
	Behrman, 2004 ¹³		60–180	

life.⁴⁹ The normal opening pressure in neonates also differs from that of older children. Kaiser and Whitelaw⁸⁴ found the mean pressure in normal neonates to be 38 mm H₂O (SD 19 mm). If one considers abnormal to be greater than two standard deviations above the mean, then based upon these results, then above 76 mm H₂O would be an elevated CSF opening pressure in a neonate.

In unusual cases, CSF hypovolemia can occur from an LP fluid leak in children.^{100,133} Resulting “post-LP” headaches are readily treated with an epidural blood patch.¹³³

IX. Treatment

Despite limited understanding about the cause and pathophysiology of the disease, advances in treatment have been made in the last decade. Unfortunately, there are still no randomized, controlled, double blind prospective studies of treatment of IIH in children, and therefore, 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. Repeat lumbar punctures, although still advocated by some authors,⁶⁵ are now 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.¹⁷⁰

Most cases of pediatric IIH respond to medical management; thus, surgical management is typically reserved only for those who fail medication. We have seen rare patients who have responded to one spinal tap with resolution in papilledema and other signs and symptoms without need for any pharmacologic or surgical therapy.

A. MEDICAL MANAGEMENT

Acetazolamide and furosemide are the drugs most often used in the medical management of pediatric IIH.³⁶ Acetazolamide, a carbonic anhydrase inhibitor, is thought to reduce the rate of cerebrospinal fluid production, and it is generally the first-line treatment choice in patients with IIH. In children, we usually use an oral dose of 15 mg/kg/day in two to three divided doses, until headache, disk swelling, and visual field abnormalities resolve—typically in 3 to 9 months. Many pharmacies can prepare a syrup formulation for younger children. Common dose-related side effects include GI upset; paresthesias involving the lips, fingers, and toes; anorexia; and electrolyte imbalance (metabolic acidosis). Kidney stones are rare, and aplastic anemia is exceedingly

uncommon. We do not monitor electrolytes as children are usually asymptomatic from the acidosis. When the side effects become intolerable, the dose is lowered, or acetazolamide is replaced with furosemide 0.3–0.6 mg/kg per day. There are reports of combining acetazolamide with furosemide to produce additive results and reduce pressure more effectively than just acetazolamide alone.¹⁶²

If acetazolamide or furosemide fail, topiramate (1.5–3.0 mg/kg per day in two divided doses, and no more than 200 mg/day), may be used, particularly when the child is obese. Topiramate is an antiepileptic medication with secondary carbonic anhydrase activity. The use of this medication in IIH is relatively new,⁴⁸ and it is unclear whether it is superior to acetazolamide in reducing CSF pressure. However, topiramate has the added benefit of appetite suppression and weight loss in many patients, it is excellent for treatment of chronic daily headache, and it has been used safely for years in children with epilepsy. The dosage should be built up slowly over weeks (25 mg/week) to reduce the risk of cognitive side effects, which are more likely to occur with rapid dose escalations and at doses higher than 200 mg/day.¹⁸³ Zonisamide, another drug with secondary carbonic anhydrase activity and appetite suppression, may be used in similar doses if the side effects of topiramate are not tolerated.

In acute situations when visual loss is severe, the combination of oral acetazolamide and IV methylprednisolone 15 mg/kg can be used when surgery is not immediately available.¹¹¹ The use of chronic steroids, however, should be avoided.

B. HEADACHE MANAGEMENT

Headaches usually resolve with reduction in cerebrospinal opening pressure. If needed, additional pain management is usually accomplished with conventional headache prophylaxis and symptomatic headache medications.⁵⁸ Daily medications that are often used in children with headaches include beta blockers such as propranolol and tricyclic antidepressants such as nortriptyline. Sodium valproate can be used, but in our experience is more useful for migraine than for causes of chronic daily headache. Caution should be applied if nortriptyline and sodium valproate are used because of their potential for weight gain, which should be avoided in patients with IIH.¹²² For this reason, topiramate and zonisamide, as previously mentioned, may be preferable for headache prophylaxis in IIH. Abortive medications for headache that can be used include acetaminophen or non-steroidal

anti-inflammatory agents such as ibuprofen or naprosyn sodium. More migraine specific triptan drugs such as sumatriptan, rizatriptan, and eletriptan are not typically used in patients with IIH.

Unfortunately, even with aggressive medical management, headaches may persist in some children.¹⁵⁸ Although many of these headaches may be a result of analgesic overuse and rebound headaches, in most cases, the reasons for persistent headaches are not well understood. CSF shunting may be necessary in cases of refractory headache.

C. SURGICAL MANAGEMENT

The two major surgical options in the modern management of IIH are optic nerve sheath fenestration and CSF shunting.

Optic nerve sheath fenestration (ONSF) is most widely used when vision loss is severe or progresses despite medical management. Only one case of pediatric ONSF in an 11-year-old boy with lateral sinus thrombosis was reviewed by Lessell,¹⁰⁷ but over the last decade, other reported cases of pediatric patients with IIH undergoing ONSF have been mentioned in the literature.^{63,90,104,123,184} Both lateral and medial approaches have been used. At least three-quarters of children were noted to experience resolution of optic disk edema,^{104,184} and visual acuity and visual fields stabilized or improved in most patients.⁶³ Furthermore, about 50% of those with unilateral surgery experienced bilateral improvement in visual acuity, but the mechanism for this is unclear.^{90,104,184} Unfortunately, initial success of surgery does not guarantee permanent visual correction. Of the 25 children cited in the literature who required ONSF, three had deterioration of vision postoperatively.^{104,123,184}

Cerebrospinal fluid shunting is preferred for those children who have intractable headaches as well as visual loss and papilledema unresponsive to ONSF. Although various shunting procedures have been experimentally used, including cisterna magna shunting,⁸¹ lumboperitoneal (LP) shunting seems to be the most successful in alleviating patients' symptoms.¹⁴⁹ The procedure, however, is associated with various complications including shunt obstruction,^{28,44} lumbar radiculopathy,^{28,44} infection,¹⁷ as well as tonsillar herniation.²⁸ Children, specifically, may be at higher risk for developing complications, possibly secondary to increased mechanical stress (growth) or the size of the shunt tubing in the thecal sac.^{28,44} In a recent study focusing on the pediatric population, 9 out of 10 patients experienced improvement in symptoms, but 7 required a total of 16 revisions as a result of shunt migration, obstruction, and tube fracture.²⁸ Duration of shunt

life varies. In one report, shunts lasted only 6 months, with an average time to failure of 9 months;¹⁵³ in another, they lasted an average of 18 months.¹⁷ Additionally, LP shunting has failed to halt progressive vision loss in some cases.²⁸ Unfortunately, to date there are no reliable risk factors that predict poor shunt tolerance, and the long-term outcome of visual function after LP shunting has yet to be studied systematically.

Because of technological advances, ventriculoperitoneal (VP) shunting has been more widely used even in patients with relatively small ventricles.¹⁹ The authors of one study¹⁹ concluded that the revision rate was less with VP compared with LP shunting.

At this time, of the surgical procedures, ONSF is preferred when vision loss is the major issue. ONSF is felt to be more effective and is thought to have fewer complications than LP shunting. In the future, prospective randomized trials comparing LP shunting and ONSF in children will be crucial in order to better understand the clinical indications for each procedure. Such a study in adults is being planned.

X. Outcome

As mentioned earlier, at presentation, visual acuity loss is reported in 6–20% of pediatric cases,^{7,29,142,158,202} and visual field loss occurs in up to 91% of cases.^{7,29,92,158} With prompt diagnosis and medical management, most children with mild-to-moderate disk swelling and visual field defects have complete resolution of disk swelling and visual abnormalities.⁷ According to one author,²⁹ pediatric IIH responds relatively rapidly to treatment, with resolution of papilledema in an average of 4.7 months. Visual acuity changes associated with macular abnormalities also usually get better with treatment, but resolution often follows improvement in visual field by several months. Reports suggest that despite treatment, permanent loss of visual acuity occurs in 0–10%^{29,92,142,202} and visual field loss persists in 17%.¹⁴² As alluded to previously, one recent report suggested that pubertal patients had a less favorable visual outcome than prepubertal, teenage, and adult patients.¹⁷⁵

The recurrence rate is low (between 6% and 22%).^{29,92,142,202} According to one study's survival analysis,⁹³ recurrences are rare during the first year, especially while on treatment. The same study argues that visual acuity is usually preserved in all patients without recurrence, but is not in those with recurrences. In our experience, recurrences seem to occur in obese adolescents who lose weight initially as part of their treatment, then regain it.

XI. Conclusion/Diagnostic Criteria for Pediatric IIH

Our understanding of pediatric IIH has been refined since Dr. Lessell's review in 1992. Recent studies' use of rigorous methodologies and standard definitions has elucidated distinct demographic trends. Specifically, the incidence of IIH seems to be increasing among adolescent children, and within older children its clinical picture is similar to that of adult IIH. Within younger age groups there are more boys and nonobese children who may develop IIH. Although the pathogenesis of the disease still remains unclear, IIH among young children has been associated with several new etiologies, including recombinant growth hormone and all-trans-retinoic acid. More modern neuro-imaging techniques such as MRI and MRI-venograms are being used to exclude intracranial processes. Although most cases of pediatric IIH improve with medical treatment, those who have had visual progression despite medical treatment have undergone optic nerve sheath fenestration and lumboperitoneal shunting.

Because IIH in young children appears to be a different disorder than in adolescents and adults, separate diagnostic criteria for younger children are warranted. This seems best accomplished by modifying the published standard criteria for IIH in adults.^{57,168,191}

Firstly, pediatric neuro-ophthalmologists and IIH experts are seeking to restrict the term "pediatric" for younger children only. As it is generally used, the term "pediatric" can be confusing. Although 18 years is the legal limit for childhood, from a biologic perspective, puberty is a more accurate marker for the completion of this phase of growth. Although the Tanner staging system is a well-known and acceptable method of determining a child's sexual maturity, there is a great variation in the progression of biological pubertal changes in both boys and girls.^{120,121} Furthermore, most ophthalmologists, neurologists, and neuro-ophthalmologists would feel uncomfortable performing a genital and complete physical exam thorough enough for complete Tanner staging (Table 3). Therefore, we believe it may be more practical for non-pediatricians and non-gynecologists to screen for any pubertal changes by history in determining whether puberty has commenced. For instance, one could simply ask a female patient or the parent whether pubic hair, breast enlargement, or menstrual cycle has appeared, without a genital examination or plotting of the growth curve. Boys or their parents can be asked about pubic hair. The term "pediatric" IIH would then be reserved for prepubertal children

TABLE 3

Patterns of Pubertal Development in Boys and Girls

Event	Female (median age in years ^a)	Male (median age in years ^a)
Breast development	11.2	–
Testicular development	–	11.6
Pubic hair development	11.7	13.4
Peak height velocity	12.1	14.1
Menarche	13.5	–
Adult public hair configuration	14.4	15.2

Data from Marshall and Tanner.^{120,121}

^aStandard deviation of one year.

who have yet to develop any secondary sexual characteristics.

Secondly, reversible cranial nerve palsies have been convincingly documented in several children with IIH, so it would seem reasonable to include children with these signs. Also, to re-emphasize that cortical function should be intact in IIH, children should be required to have a normal sensorium.

Finally, as alluded to earlier, CSF opening pressures are different in children than in adults, and CSF content and pressure in neonates have different normative values. For these reasons, we suggest modifying the diagnostic criteria to allow for these normal variations.

Therefore, in Table 4 we propose criteria for the diagnosis of pediatric IIH. We hope that these new criteria will allow more accurate diagnoses as well as more directed future research into the pathogenesis, diagnosis, and treatment of this disorder in children.

XII. Method of Literature Search

To draft this review, a thorough Medline search of all English articles between 1992 and 2006 was conducted. Search terms included: *pediatric pseudotumor cerebri*, *pediatric idiopathic intracranial hypertension (IIH)*, *pediatric neoplasms*, *pediatric pseudotumor cerebri diagnosis*, *pseudotumor cerebri AND drug therapy*, *IIH AND drug therapy*, *pseudotumor cerebri AND headache*, *IIH AND headache*, *pseudotumor cerebri AND acetazolamide*, *IIH AND acetazolamide*, *pseudotumor cerebri AND corticosteroids*, *IIH AND corticosteroids*, *pseudotumor cerebri AND MRI*, *IIH AND MRI*, *pseudotumor cerebri AND MRI venogram*, *IIH AND MRI venogram*, *pseudotumor cerebri AND segmental sinus stenosis*, *IIH AND stenosis*, *pseudotumor cerebri AND lumbar peritoneal shunting*, *IIH AND lumbar peritoneal shunting*, *pseudotumor cerebri AND optic nerve sheath fenestration*, *IIH AND optic nerve sheath fenestration*,

TABLE 4

Proposed Diagnostic Criteria for Pediatric IIIH

1. Prepubertal^a
2. If symptoms or signs presents, they may only reflect those of generalized intracranial hypertension of papilledema. Normal mental status.
3. Documented elevated intracranial pressure (age appropriate) measured in the lateral decubitus position.
Neonates: > 76 mm H₂O
Age less than 8 with papilledema: > 180 mm H₂O
Age 8 or above or less than 8 without papilledema: > 250 mm H₂O
4. Normal CSF composition except in neonates who may have up to 32 WBC/mm³ and protein as high as 150 mg/dl.
5. No evidence of hydrocephalus, mass, structural, or vascular lesion on MRI, with and without contrast, and MR venography. Narrowing of the transverse sinuses is allowed.
6. Cranial nerve palsies allowed if they are of no other identifiable etiology and improve with reduction in cerebrospinal fluid pressure or resolution of other signs and symptoms of intracranial hypertension.
7. No other identified cause of intracranial hypertension.

Table modified from Friedman and Jacoben⁵⁹ and Smith.¹⁶⁸

^aIn boys, supported by no evidence of pubic hair. In girls, supported by lack of breast development, growth of pubic hair, or menarche (Table 3).

pseudotumor cerebri AND visual outcome, and IIIH AND visual outcome.

In addition to searching Medline, all related articles cited in reference lists of other articles were included. Non-English articles have not been included, nor have abstracts. Given that the last review was published in 1992, only a few select articles prior to 1992 have been included for historical purposes, but otherwise this review focuses mainly on articles published since 1992.

Finally, only those articles available through the University of Pennsylvania Library and Children's Hospital of Philadelphia systems (electronic or paper), without cost from journal Web sites, or by direct communication from the authors, were used.

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