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ADVANCES IN PEDIATRIC RESEARCH

Idiopathic intracranial hypertension without papilledema in children: A case series

Kaliopy Matheos [1,2], **Shuan Dai** [1,2*]

1 Department of Ophthalmology, Faculty of Medical & Health Sciences, University of Auckland, Auckland, New Zealand **2** Department of Ophthalmology, Auckland District Health Board, Greenlane Clinical Center, Auckland, New Zealand

Abstract

Papilledema has long been considered a hallmark of idiopathic intracranial hypertension, a disease defined by elevated intracranial pressure with indiscernible etiology. Papilledema is often seen in the pediatric population, and as such can lead to delays in diagnosis, and often misdiagnosis. Here, we describe three children who were confirmed to have idiopathic intracranial hypertension with raised intracranial pressure by repeated lumbar puncture or intracranial pressure monitoring, normal neuroimaging and absence of papilledema. All three cases had atypical clinical presentations with visual disturbances or photophobia. The patients had a normal body mass index. This case series demonstrates that idiopathic intracranial hypertension can manifest in the absence of clinically obvious papilledema, and has, as such, the potential to cause permanent visual loss if the diagnosis is missed.

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* Email: shuand@adhb.govt.nz

Introduction

Idiopathic intracranial hypertension (IIH), also known as pseudotumor cerebri, is defined as elevated intracranial pressure not associated with any identifiable etiology [1, 2]. The Modified Dandy Criteria [1, 2], have been widely used for the diagnosis of IIH. However, these criteria pertain to adult IIH; Rangwala et al. [3] proposed modifications of these criteria for use in suspected pediatric IIH [3]. Although IIH is not common in children, loss of vision is the most serious complication. Papilledema is widely considered a hallmark of IIH, and IIH in the absence of papilledema, while uncommon, is a recognized condition in adults, usually presenting with clinical features of chronic daily headaches or migraine [4]. We describe three children, who presented to our service, who had a confirmed diagnosis of IIH despite the absence of papilledema.

Case series

Case 1

A nine-year old girl presented with a two-month history of decreased vision and photophobia, which had initially been treated as allergic eye disease. Two years previously she had been seen by an optometrist for a sudden drop in vision and had been prescribed corrective lenses for astigmatism. On presentation she was normotensive, with a body mass index (BMI) of 17.5 (weight 44kg, height 1.58m). Neurological examination was normal, including that of the cranial nerves. Ophthalmic examination found decreased visual acuity (6/24) in each eye, which did not improve with refraction. She also had a reduction in color vision in both eyes and was able to correctly identify only 10 of 14 plates in an Ishihara test. There was no evidence of swelling of the optic nerves; however, as shown in the photos taken at

presentation, there was mild, bilateral temporal atrophy (Figure 1a and 1b), which was also demonstrated by optical coherence tomography (OCT) of the retinal nerve fiber layer (Figure 1c). Formal automated perimetry was unreliable. OCT of the maculae, and electroretinogram (ERG) and visual evoked potential (VEP) were normal. Coronal and axial imaging using gadolinium magnetic resonance imaging (MRI), and magnetic venography (MRV) of the brain and orbits, demonstrated bilaterally small optic nerves. The opening pressure of the cerebrospinal fluid (CSF) was measured under sedation in the lateral decubitus position, and was found to be 42 cmH_2O. CSF composition was normal. The patient began a course of acetazolamide (750mg daily), and - due to the absence of clinical symptoms - required regular CSF opening pressures to monitor her response to treatment. A second opening pressure under sedation, two-weeks after commencing treatment, was at 39 cmH_2O, and the dose of acetazolamide was increased to 1g daily. She required multiple admissions for insertion of an intracranial pressure (ICP) monitor to gauge treatment response. Initially, ICP was measured between 22 and 28 with intermittent spikes to 32 on treatment, with eventual measurements stabilizing between 18 and 25 mmHg. One month following commencement of medical treatment, her visual acuity had improved (6/9) in each eye and she had full color vision. The appearance of her optic nerves remained unchanged. She required treatment for 15 months with 1g daily acetazolamide before her ICP was normalized and the medication tapered off. Her ICP remained normal with no recurrence of symptoms four years after cessation of treatment.

Case 2

A five-year old boy presented with a four-day history of increasing headaches and double vision. He was normotensive with a BMI of 16.8 (weight 25kg, height 1.22m) and was systemically well. Ophthalmic examination showed his visual acuity to be 6/7.5 in each eye, with a full range of ocular motility and a large angle alternating esotropia of 35 prism diopters. Cycloplegic refraction showed no evidence of refractive error and examination of the fundus showed normal optic nerves with no evidence of swelling. MRI demonstrated an area of increased subdural space surrounding each optic nerve with non-specific enhancement. CSF opening pressure was measured in the lateral decubitus position under general anesthetic and was found to be 27 cmH_2O.

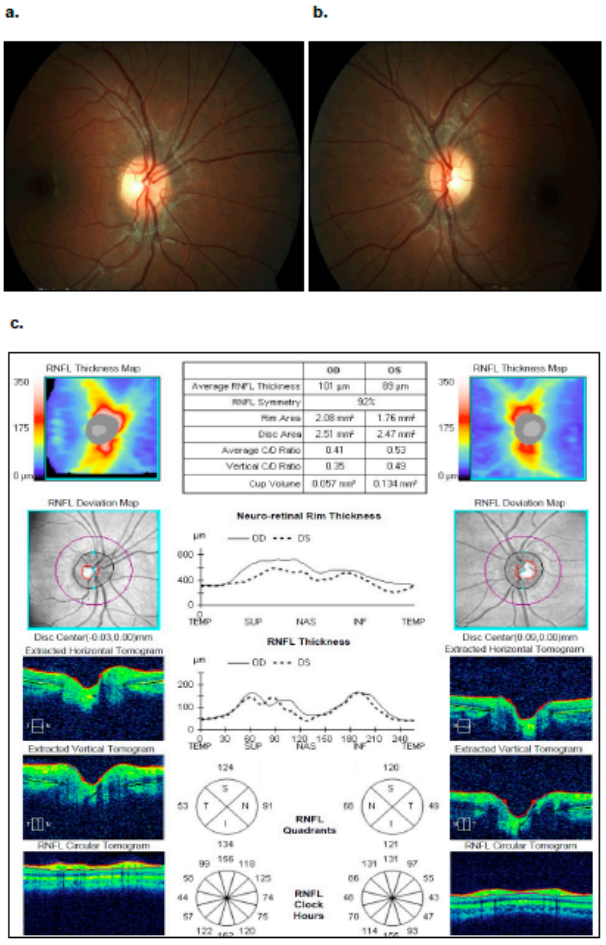

Figure 1. Optic nerve appearance, as seen in Case 1 at presentation

(a) & (b) Right and left optic nerve photos taken at presentation. These demonstrate the clear demarcation of the both disc margins in the absence of any clinically evident optic nerve head swelling. Further, temporal pallor of both the right and left optic nerve heads can be seen. (c) The Optical coherence tomography scan of the retinal nerve fiber layer (RNFL), also taken at presentation, demonstrates loss of the neuroretinal rim at the temporal sector of the both the right and left nerve optic nerve*, supporting the clinical finding of temporal optic nerve head pallor

*when compared to age-appropriate normative values as reported by Al-Haddad et al. [21].

He began treatment with acetazolamide (250mg daily) and his headaches resolved. He was eventually tapered off acetazolamide over an eight-month period; his alternating esotropia remained and he required surgical correction. Post-operatively, the patient remained asymptomatic with no recurrence of his strabismus.

Case 3

A ten-year old girl presented with a history of increasing intractable headaches over a three-month period, and photophobia. She was normotensive with a BMI of 17.7 (height 1.45m, weight 37.3kg). Ophthalmic examination found an unaided visual acuity of 6/6 in both eyes and a physiological right anisocoria. Neurological examination, including cranial nerve function was normal and she had full color vision according to an Ishihara plate test. Her optic nerves appeared normal (Figure 2a and 2b) with no evidence of edema, but absence of spontaneous venous pulsations was noted. There was no deficit of formal perimetry, and OCT of the retinal nerve fiber layer was normal (Figure 2c). MRI and MR venography of the brain and orbits was normal. CSF opening pressure was measured in the lateral decubitus position under sedation and found to be 36 cmH_2O with normal CSF composition. Despite commencing treatment with acetazolamide (500mg daily), her headaches continued. A repeat CSF opening pressure (again, measured in the lateral decubitus position under sedation), was measured at 52 cmH_2O, and the acetazolamide dose was increased to 2g daily. Attempts over a 12-month period to reduce the dose of acetazolamide were unsuccessful, with rebound headaches and persistently elevated ICP (29 cmH_2O). She began concurrent furosemide treatment (20mg daily), which effectively relieved her headaches. Subsequent ICP monitoring showed that her ICP stabilized to 15 mmHg with intermittent spikes to 20 mmHg. She was successfully tapered off acetazolamide and furosemide over a six-month period.

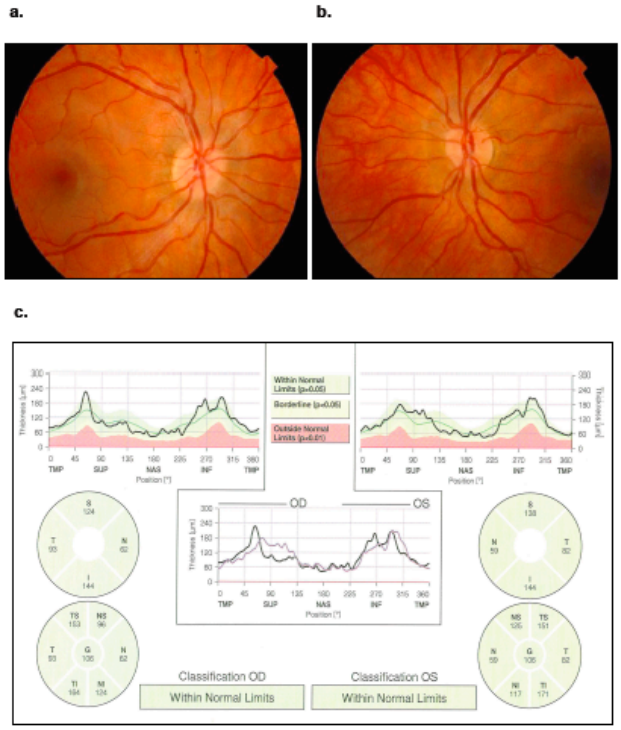

Figure 2. The optic nerve appearance in Case 2, at presentation

(a) & (b) Right and left optic nerve head photos taken at presentation. These demonstrate a clear demarcation of both disc margins and the absence of any vascular obscurations in the absence of clinically evident optic nerve head swelling. (c) The optical coherence tomography of the retinal nerve fiber layer, also taken at presentation, demonstrates normal thickness of the neuroretinal rim **, supporting the clinical observation of an absence of obvious disc swelling clinically.

** *when compared to age-appropriate normative values, as reported by Al-Haddad et al. [21].*

Discussion

Pediatric idiopathic hypertension is a rare condition. We report three pediatric cases in which a diagnosis of IIH was made despite the absence of papilledema. In each case, the absence of papilledema was confirmed by an ophthalmologist and documented with photos of the optic nerves. In addition, two of the three cases had OCT retinal nerve fiber layer analysis. CSF pressures were measured under general anesthesia (Cases 1 and 3) or sedation (Case 2) by a pediatric neurologist, with the patient in the lateral decubitus position. All three patients discussed in our series had raised ICP readings on at least two separate

occasions. None of our patients demonstrated papilledema at any stage during the course of their treatment.

The absence of papilledema in pediatric IIH is not well recognized, and can as such, pose a risk of delayed diagnosis [5, 6]. The exact prevalence of IIH without papilledema is unknown. Digre et al. [7] compared the characteristics of 353 patients with IIH (ages ranging from 10 to 56 years), with and without papilledema, finding 5.7% of patients diagnosed with IIH (ICP ranging from 26 to 42 cmH_2O), did not have papilledema. In pre-pubertal children, intracranial hypertension without a secondary cause is even less frequent when compared to a post-pubertal or adolescent population [8, 9]. Unlike adults, pre-pubertal IIH has no predilection to sex and no association with obesity [8, 9]. All three of the patients in our series were under the age of 12 (pre-pubertal) with normal to low BMIs; two were female, and presentations varied with two of the three patients having severe headaches.

In our case series, Patient 1 presented with a deterioration in visual acuity and color vision. While there was no evidence of papilledema, both optic nerves demonstrated mild temporal optic nerve pallor, suggesting the possibility of some degree of atrophy, which was supported by OCT measurement of the RNFL. Classically, OCT devices have an integrated normative database for adult subjects (>18 years). Al-Haddad et al. [21] reported normative values for RNFL analysis in children using spectral domain OCT (Cirrus, Carl Zeiss). Based on these values, (the normative range for temporal RNFL in a child aged 6-9 years is a mean of 69 µm, range 56-87 µm; 5^{th}-95^{th} percentile), our patient demonstrated temporal RNFL thickness outside the normative range (53µm OD and 49µm OS), suggesting atrophic changes (Figure 1c). Although optic atrophy is a classic complication of papilledema in IIH [10], Patient 1 developed optic atrophy despite the absence of any clinically evident papilledema. Visual loss in patients with IIH without papilledema has been suggested to be of a non-organic cause or functional cause [7]. Digre et al. [7] found that patients with IIH without papilledema were more likely to manifest non-physiologic constriction of their visual field [7]. Patient 1 demonstrated generalized constriction on formal perimetry, which was unreliable, and also the presence of severe but unexplainable photophobia. Both of these findings may be postulated as functional. However, a functional cause does not explain the subsequent finding of markedly and persistently elevated ICP and temporal thinning of her optic nerves demonstrated on OCT, which is postulated as a likely a consequence of chronically raised ICP. Other mechanisms have been proposed for visual loss in the absence of papilledema, including an acquired or congenital optic nerve sheath abnormality [11], or posterior optic nerve compression. A raised ICP is postulated to potentially produce intracranial or retrobulbar optic nerve compression in the presence of an anatomic compartmentalization of the subarachnoid space around the optic nerve [12, 13]. In effect, this would prevent a CSF pressure gradient from reaching the retrolaminar portion of the nerve, producing compression of the retrobulbar optic nerve with no clinical evidence of optic disc swelling [12]. Another postulated mechanism, as many patients with IIH have cerebral venous hypertension, is ischemia of the posterior optic nerve secondary to impaired venous drainage [14]. Despite atypical cases of visual deterioration, extreme caution should be used before attributing visual loss in IIH to raised ICP in the absence of papilledema. In our patient, careful and thorough investigations found no other cause for her visual deterioration; her visual acuity improved once ICP was stabilized with medical treatment.

While visual loss is uncommon in pre-pubertal IIH, the most common presenting feature in these children is a strabismus secondary to a sixth nerve palsy [1]. Patient 2 in our series presented with an acute, large angle alternating esotropia of 35 prism diopters, but had a full range of eye movements. Acute esotropia is not typical for IIH, but has been well described in patients with a raised ICP due to an acute obstructive hydrocephalus caused secondary to a tumor [15]. Imaging and thorough investigation of Patient 2 did not reveal any intracranial lesions, and commencement of acetazolamide treatment stabilized his ICP and provided relief of his headaches prior to eventual surgical correction of his esotropia.

Chronic migraine has been associated with IIH in the absence of papilledema [16, 17]. Vieira et al. [16] described a high incidence (10%) of IIH without papilledema in patients with a history of chronic

migraine. Wang et al. [17] found that the headache characteristics of these patients were identical to patients with chronic headaches and normal ICP. These clinical similarities can be the cause of delays in the diagnosis of IIH when there is an absence of papilledema. In our series, Patient 2 had undergone an initial lumbar puncture without documentation of an opening pressure, as a diagnosis of IIH was thought unlikely due to the absence of papilledema. He required further anesthesia and a second lumbar puncture to confirm a diagnosis. Wraige et al. described two cases of pediatric IIH without papilledema, in which diagnosis was delayed for more than one year [5]. IIH should be considered in children with a history of chronic daily headache that is resistant to conventional treatment and severe enough to interfere with normal daily routine and function, even in the absence of papilledema.

Non-specific radiological abnormalities can occur with IIH and may assist in establishing a diagnosis. Empty sella and non-specific enhancement abnormalities of the optic nerves are two such findings, both occurring as a consequence of chronically raised ICP [18]. Patient 2 in our series was noted to have a subtle enhancement surrounding the optic nerves on MRI, suggesting an increase in the subdural space. This led to the suggestion of IIH as a diagnosis, and eventually the CSF opening pressure procedure was repeated.

The management of IIH is aimed at relieving the clinical symptoms related to intracranial hypertension, and the prevention of visual loss [19]. In this series, medical therapy was eventually successful in treating the symptoms of IIH in all our patients. Unfortunately, despite aggressive management, headaches can often persist in some children, and the pathophysiology of persistent headache is not well understood [20]. Digre et al. [7] found that patients with IIH but no papilledema, were more likely to require shunting to treat intractable headaches. This suggests that the headaches in IIH in the absence of papilledema may be more refractory to standard medical treatment compared to headaches in IIH with papilledema. Both Patients 1 and 3 in our series had persistently raised ICP, measured on at least four separate occasions. Both cases required more than 12 months of high dose acetazolamide treatment, and Case 3 required additional treatment with furosemide to eventually control the raised ICP. None of our cases required insertion of a shunt, with eventual optimal clinical outcomes, suggesting that perhaps higher doses of acetazolamide and a longer course of treatment may still be effective in treating children with IIH without the need for surgical intervention.

This case series highlights the need for an awareness that papilledema is not an absolute requirement when considering IIH in children. IIH in children is rare and can have presenting characteristics that differ from adult IIH. Childhood IIH has no sex predilection and obesity is uncommon in pre-pubertal patients. Prompt diagnosis and management is important to avoid long-term visual loss. Non-specific findings on MRI may assist with prompt diagnosis. The possibility of IIH needs to be considered in children with chronic headache, as medical and surgical management to lower CSF could assist with symptom control and prevent further progression of the condition.

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