CASE REPORT

Idiopathic Intracranial Hypertension in a Mother and Pre-pubertal Twins

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ABSTRACT

Idiopathic intracranial hypertension is a syndrome of elevated intracranial pressure without an identifiable cause. The majority of cases appear to be sporadic, and incidence is highest in obese women of childbearing age. The role of genetics in the pathophysiology of the disease is unclear, and familial cases are rare. We report a familial occurrence in a mother and her twin, 5-year-old sons.

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Introduction

Idiopathic intracranial hypertension (IIH) is a condition characterized by elevated intracranial pressure (ICP) without an identified causative factor.^{1,2} The diagnostic criteria were first published by Walter Dandy in 1937³ and include papilloedema, normal neurologic exam except cranial nerve abnormalities, normal cerebrospinal fluid (CSF) composition, and a lumbar puncture (LP) opening pressure greater than 25 cm of water. Most recently, Friedman et al revised the criteria in 2013 to require ‘no evidence of hydrocephalus, mass, or structural or vascular lesion on magnetic resonance imaging (MRI) in the absence of medical conditions and medications that can mimic IIH’.⁴

While the first case of IIH was reported over a hundred years ago,¹ the aetiology is still unknown. The role of genetic factors in the pathophysiology of IIH is unclear, and familial cases are rarely identified. A study by Corbett in 2008 identified 11 affected families and compared them to 13 previously reported familial cases. Of the 24 total cases, 16 were parent–child combinations and 8 were sibling–sibling. To our knowledge, occurrence in pre-pubertal, dizygotic twins has not been reported. This report describes a familial occurrence of IIH affecting a mother and her male, dizygotic twin sons.

Report of cases

Mother. In October 2011, a 22-year-old obese female with a past medical history of depression, tobacco use, and preeclampsia, who was 18 months post-partum from a twin gestation, presented with intermittent headaches and blurred vision in the left eye (OS).

Examination showed visual acuities of 20/20 right eye (OD) and 20/20 OS. Colour vision and pupil examination were normal. Automated perimetry demonstrated an enlarged blind spot OD and an inferior altitudinal defect OS. Dilated fundoscopic exam revealed Frisen grade 4 optic disc oedema, both eyes (OU). Brain MRI showed a partially empty sella, widened perioptic spaces, and flattening of the globes OU. Head magnetic resonance venography (MRV) demonstrated narrowing of the distal right transverse sinus but no evidence of thrombosis. LP showed an opening pressure of 32 cm H₂O with normal CSF constituents confirming the diagnosis of IIH. She did not have any known predisposing factors to ICP, such as Addison’s disease, hypoparathyroidism, steroid withdrawal, tetracycline use, or vitamin A toxicity.

The patient was followed over the next 6 years on and off acetazolamide. Her symptoms worsened during periods of significant weight gain and improved with weight loss. On her most

recent follow-up in June 2017, automated perimetry was full OD and demonstrated nasal step OS. Fundus exam showed Frisen grade 2 papilloedema OD and grade 1 OS.

Twin A. In September 2015, her 5-year-old son was noted to have decreased visual acuity on routine school eye screening. He had been complaining of headaches two times a week for several months. He denied double vision or squinting. His past medical history was significant for preterm birth, and his weight-for-age was in the 5th percentile.

Best-corrected visual acuities were 20/40 OU. Colour vision, pupils, and confrontation visual fields were normal. There were no motility defects. Both optic nerves were elevated with blurring of the disc margins. B-scan ultrasound was questionable for optic disc drusen, and the mean retinal nerve fibre layer (RNFL) was 171 μm OD and 174 μm OS. Volume scans did not show anterior deflection of the retinal pigment epithelium. He was initially diagnosed with probable pseudopapilloedema. Two months later, his mean RNFL was 122 μm OD and 126 μm OS. This significant change prompted a brain MRI that showed a Chiari malformation with 8 mm of tonsillar herniation, a partially empty sella, widened perioptic spaces, and flattening of the globes. He had no visual complaints, and since his optic nerve swelling had decreased, he was observed.

In January 2016, since his RNFL increased to 126 μm OD and 136 μm OS, an unsedated LP in the left lateral decubitus position was performed showing an opening pressure of 34.5 cm H_2O with normal CSF composition. He did not have any known predisposing factors to ICP. He was started on acetazolamide 125 mg twice daily. At his last visit 1.5 years later, his visual acuity was 20/20 OD and 20/40 OS. He admitted to taking the acetazolamide occasionally. His refraction showed asymmetric hyperopic changes, and he was referred to paediatric ophthalmology. There was bilateral blurring of the margins and Frisen grade 2 disc oedema OU. His mean RNFL was 117 μm OD and 126 μm OS.

Twin B. In February 2016, an optometrist referred the 5-year-old fraternal twin brother for asymptomatic optic disc elevation. His past medical history was also significant for preterm birth, and

his weight-for-age was in the 50th percentile. He denied symptoms of increased intracranial pressure.

On examination, his visual acuities were 20/25 OU. Colour vision, pupils, and confrontation visual fields were normal. There were no motility defects. The optic nerves were slightly elevated with blurred margins bilaterally, and the mean RNFL was 116 μm OD and 117 μm OS. Enhanced-depth imaging OCT was negative for drusen. He was diagnosed with probable pseudopapilloedema and instructed to return for a repeat RNFL in 2 months.

Two months later, the patient developed occasional headaches and was found to have bilateral optic disc oedema, Frisen grade 1 OD and 2 OS, with a mean RNFL of 123 μm OD and 179 μm OS. Brain MRI showed a partially empty sella, widened perioptic spaces, and flattened globes. Brain MRV showed no venous sinus thrombosis or narrowing of the transverse sinuses. LP under conscious sedation in the left lateral decubitus position showed an opening pressure of 43 cm H_2O with normal CSF constituents. He did not have any known predisposing factors to ICP. He was diagnosed with IIH and started on acetazolamide 125 mg twice daily. At his last visit in June 2017, his visual acuities were 20/20 OU. He was also taking acetazolamide only occasionally. His optic nerves were not swollen and his mean RNFL measured 114 μm OD and 126 μm OS.

Discussion

The incidence of IIH in the general population is 1.8 per 10,000 and is increasing with the obesity epidemic.⁵ The typical patient is an obese female of childbearing age, with the incidence being twenty times higher in women age 20–44 who are greater than 20% over their ideal body weight.^{1,5} Headache is the most common presenting symptom, with transient vision disturbances being second.¹ Other symptoms include diplopia, pulsatile tinnitus, vision loss, retrobulbar pain, nausea, and vomiting, however, IIH can be asymptomatic. Bilateral papilloedema is the most common sign on physical exam,^{1,5} but sixth nerve palsy may also be present.⁶ Despite affecting a specific demographic, the aetiology of IIH remains unknown.

The majority of IIH cases appear to be genetically unrelated. The first familial case of IIH was reported in 1969 where two sisters, ages 19 and 24, presented with increased ICP and papilloedema within 3 months of each other.⁷ The study by Corbett is currently the only published review that has looked at multiple families with IIH and suggests an autosomal dominant pattern of inheritance.⁸ All of the patients in Corbett's cohort had adult-onset symptoms, and only three patients in the cohort of previously reported familial cases had pre-pubertal onset. Most patients in both cohorts were obese.⁸ After review of these cases, Corbett suggested the role of a 'genetic clock' where age of disease onset tends to be similar between family members.⁸ Given the predilection of IIH among obese patients, it could be argued that obesity is shared in these family members and predisposes them to developing IIH, rather than IIH itself being inherited. More likely, this represents a combination of environmental and genetic factors. In our case, the mother was obese, but the twins were pre-pubertal, not obese, and presented remarkably close together, with only 5 months separating their diagnoses.

IIH is rarely diagnosed in childhood, and it has different characteristics than the adult form.¹ Although 'pediatric' typically refers to patients 18 years old and under, a better demarcation for IIH is puberty, because post-pubertal paediatric cases usually exhibit female predominance and a strong association with obesity similar to the adult form.⁹ In pre-pubertal patients, there is no gender predilection and no association with obesity.¹⁰ While headache is still the most common presenting symptom, children often present with cranial nerve abnormalities resulting in strabismus and diplopia.^{9,10} Pre-pubertal cases, similar to adult cases, are at risk for vision loss.¹⁰

To our knowledge, there have been no reported cases of IIH occurring in pre-pubertal dizygotic male twins. There are also no reports of IIH affecting multiple family members with pre-pubertal onset. While the mother in our case was an obese female of childbearing age and met the typical demographic of IIH, the twins were atypical for the standard adult IIH presentation with regard to gender, age of onset, and body habitus. The atypical nature of their demographics suggests a genetic

component to this presentation. After the second son was diagnosed with IIH, it was postulated that there could be an environmental factor influencing their disease process. The father and another brother were examined and did not have papilloedema, which made this less likely. Secondary causes of IIH were considered, such as vitamin A toxicity or an inherited endocrine disorder, however, no evidence of a secondary aetiology was found.

Paediatric cases are diagnosed infrequently, and familial cases are even more uncommon.^{11,12} Our knowledge on the role of genetic factors in the disease process is limited, and most of the knowledge we have has been extracted from retrospective studies and case reports. To our knowledge, no prospective, systematic effort has been made to identify affected families. The incidence of familial cases could be underestimated due to an under-recognition of paediatric cases. Diagnosis of pre-pubertal cases can be challenging, because they often do not exhibit the typical IIH demographic,^{9,10} and young children may have difficulty articulating their symptoms.¹⁰ A small number of patients are incidentally found to have papilloedema on dilated fundus exam,¹³ and up to 30% of paediatric cases of IIH may be asymptomatic similar to our Twin B.¹⁴ Additionally, family members are often separated by geographic location and time, which can make identification of familial cases difficult. Because of this, familial IIH may go unrecognized unless we are actively looking for disease.

In summary, this report describes a familial case of IIH in a mother and her pre-pubertal, dizygotic twin sons. To our knowledge, a familial case of IIH in pre-pubertal twins has not been reported. Because IIH can cause irreversible vision loss in both adults and children, early recognition of the disease is imperative. The diagnosis of pre-pubertal patients can be difficult, so it is important to maintain a high awareness of such cases. The twins in this case presented within 5 months of each other, which aligns with Corbett's idea of a genetic clock contributing to the age of onset. If IIH is diagnosed in a twin, evaluation of the other twin or siblings could be considered. Screening family members may help diagnose familial cases and contribute to our understanding of the potential role of genetics in the pathophysiology of IIH.

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Declaration of interest

The authors declare that there are no conflicts of interest. The authors alone are responsible for the writing and content of the article.

Support

None

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