Familial Occurrence of Idiopathic Intracranial Hypertension

Ainat Klein MD, Gad Dotan MD and Anat Kesler MD

Department of Ophthalmology, Tel Aviv Sourasky Medical Center, Tel Aviv, affiliated with Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel

ABSTRACT: **Background:** Idiopathic intracranial hypertension (IIH) is a disorder of unknown etiology. Its occurrence in the general population is 1/100,000, and 20/100,000 among overweight women of childbearing age. Familial occurrence is reportedly uncommon and not well-characterized.

Objectives: To describe a familial association with IIH.

Methods: We conducted a retrospective chart review of all familial cases of IIH examined in the neuro-ophthalmology clinic of our medical center between January 2006 and June 2013.

Results: Of a total of 520 patients with IIH, 15 had other family members with IIH (from seven different families). The family relation was a mother and daughter in two families, a brother and sister in four families, and an aunt and two first-degree cousins in the seventh family. Symptoms, course of disease, and risk factors were similar among the relatives of all seven families, except for the age at diagnosis, which was different in one family. All of the adult patients of six families were obese (body mass index 25–35 kg/m^2), and all of the members of the other family were morbidly obese. There was no association between other systemic risk factors and IIH.

Conclusions: IIH occurrence within a family is more common than previously believed, and its incidence in families is more common than in the general population. The clinical course appears to be similar in family members. Our findings suggest a genetic predisposition. Further investigation of familial cases may yield useful information on the pathogenesis and genetic nature of this condition.

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KEY WORDS: familial occurrence, genetic predisposition, idiopathic intracranial hypertension (IIH), papilledema, pseudotumor cerebri (PTC)

Idiopathic intracranial hypertension (IIH), also known as pseudotumor cerebri (PTC), is a disorder of increased intracranial pressure without clinical, laboratory, or radiologic evidence of an intracranial space-occupying lesion or cerebral sinus vein thrombosis. It predominantly affects obese women of childbearing age [1]. The pathogenesis of IIH is unknown, and suggested etiologies include irregular autoregulation of cerebral blood flow and malfunctions of cerebrospinal fluid (CSF) production and drainage. Several studies found a connection between IIH and various endocrinologic and metabolic defects [2-5]. Reports of familial cases of IIH are rare. Buchheit and colleagues [6], in 1969, were the first to report that IIH can affect more than one family member. Since then, another 18 case reports were published in the English literature, each describing one family with a few family relatives also were diagnosed with IIH. Those reports, however, have several limitations, including lack of measurement of intracranial pressure, as well as the inclusion of secondary IIH, such as that following hypervitaminosis A [7-12]. Gardner and co-authors [13] reported on fraternal twin sisters who developed IIH shortly after beginning tetracycline for treatment of acne. That team suggested that tetracycline-induced IIH may be related to an underlying genetic susceptibility, and they supported the notion of multifactorial etiologies for IIH.

Corbett [14] reported 27 IIH patients coming from 11 families. His data were the most extensive published to date, and they doubled the reported number of familial cases reported in the literature. Since familial cases constituted 11% of his cohort of IIH patients, he recommended routinely evaluating first-degree relatives of IIH patients with the aim of identifying asymptomatic family members.

IIH is currently considered a sporadic disease and no gene has been identified as the precursor of this clinical syndrome. The appearance of several recent reports that suggested a genetic factor [13,14] motivated us to evaluate the database on familial cases of IIH treated at our medical center.

PATIENTS AND METHODS

We reviewed all data of IIH patients from the neuro-ophthalmology clinic at the Tel Aviv Medical Center, between January 2006 and June 2013. Diagnosis was made according to the modified Dandy criteria: (1) presence of signs and symptoms of increased intracranial pressure, (2) absence of localizing findings on neurologic examination except those known to occur from increased intracranial pressure, (3) normal neurodiagnostic studies, except for evidence of increased cerebrospinal fluid pressure (> 200 mm H_2O), (4) normal neuroimaging, except for empty sella turcica, optic nerve sheath with filled out CSF spaces, and smooth-walled non flow-related venous sinus stenosis or collapse, (5) awake and alert patient, and (6) no other cause of increased intracranial pressure present [15,16].

Family relatives were identified through the medical history part in the medical interview, as patients are ordinarily asked about significant diseases in family relatives (e.g., genetic disease, tumors, or neurological disease). In cases in which a first- or second-degree relative was reported to have a diagnosis of IIH, it was recorded.

Patient records were reviewed for clinical details including age, gender, body mass index (BMI), systemic disease, medications, symptoms, ocular findings, imaging results, cerebrospinal fluid (CSF) opening pressure (OP) and content, course of disease, response to treatment, and final visual function.

BMI was categorized according to the WHO recommendation of ideal body weight and disease prevention [17]: underweight (< 18.5 kg/m^2), normal weight (18.5–24.9 kg/m^2), overweight (25–29.9 kg/m^2), obese (30–34.9 kg/m^2), severe obesity (35–39.9 kg/m^2), and morbid obesity (≥ 40 kg/m^2).

The study was approved by the institutional review board of the medical center.

RESULTS

Out of the 520 IIH patients treated in our clinic during the study period, a total of 15 IIH patients from seven different families were identified. The patients included 12 females and 3 males whose average age was 23 years (range 3–40). The main clinical characteristics of the patients are summarized in Table 1. They all had normal neuroimaging findings, except subtle changes considered secondary to increased intracranial pressure (ICP) as detailed in the Dandy criteria [15,16], with no evidence of sinus vein thrombosis (SVT). The CSF OP ranged from 250 to 500 mmH_2O, with normal CSF constituents in all cases.

The familial relationship was mother and daughter in two families, two siblings in four families and an aunt and two first-degree cousins in the remaining family. All of the adult patients had BMI ≥ 25 kg/m^2: two overweight, four obese, two severely obese, and two morbidly obese. With the exception of obesity, there was no correlation of risk factors presumed to contribute to developing IIH among the family members. In two families, both of the affected family members had hypercoagulation conditions (families 2 and 3), but SVT had been excluded by appropriate imaging. The symptoms and course of disease were similar between relatives in all seven families, except for age at diagnosis, which differed in two families (families 3 and 6). Nine of the patients had a benign course and improved after brief treatment with oral acetazolamide, three had a relapsing-remitting course (none were compliant with treatment), and one was lost to follow-

Table 1. Demographic and clinical characteristics of the study group (n=15)

Family number	Patient	Family relation	Age at onset, years	LP pressure, mmH_2O	BMI	Associated features	Course of disease	Final visual acuity	Visual field
1	a	Brother	3	250	20	None	Benign	6/6 BE	No defects
	b	Sister	8	300	33	None	Benign	6/6 BE	No defects
2	a	Mother	27	› 500	39	Protein C deficiency, hypertension	Benign	6/6 BE	No defects
	b	Daughter	19	250	26	Anticardiolipin	Benign	6/6 BE	No defects
3	a	Mother	35	260	30	Polycythemia vera	Relapsing-remitting, non-compliance	6/6 BE	BE inferonasal defect
	b	Daughter	14	290	30	Protein C deficiency, PCO	Relapsing-remitting, non-compliance	6/6 BE	No defects
4	a	Sister	19	320	unknown	PCO	Lost to follow-up	Lost to follow-up	Lost to follow-up
	b	Sister	20	300	37	None	Relapsing-remitting, non-compliance	6/6 RE 6/10 LE*	LE superior peripheral defect
5	a	Aunt	40?	› 250	› 40**	None	LP shunt	Lost to follow-up	Lost to follow-up
	b	Daughter	38	› 250	25	None	Optic nerve fenestration	6/6 RE 6/7.5 LE	BE peripheral constriction
	c	Cousin	31	400	48	None	Benign	6/7.5 BE	No defects
6	a	Sister	18	310	33	None	Benign	6/6 BE	No defects
	b	Brother	8	300	‹ 20	None	Benign	6/9 BE	No defects
7	a	Sister	34	› 250	34	Hypothyroidism***	Prolonged but Benign	6/6 BE	No defects
	b	Sister	39	› 250	unknown	None	Benign	6/6 BE	No defects

*Left eye is known as amblyopic, no reported deterioration

**Known to have morbid obesity necessitating gastric band

***Hormonally stable for a few years

BMI = body mass index, BE = both eyes, LE = left eye, RE = right eye, LP = lumbar puncture, PCO = polycystic ovary syndrome

up. Two patients in one family required surgical intervention. All the patients, except one, had a good final visual outcome (range 20/20 to 20/25) with no visual field defects.

DISCUSSION

We identified 15 familial cases among 520 cases of IIH in our database, representing 2.9% of our IIH cohort patients during the 8 year study period. This incidence of familial cases is more common than previously believed in the general population, and much more common than the general incidence of IIH, even among high-risk populations (young obese females). This incidence in our patient population, however, is lower than the 11% reported by Corbett [14]. The familial relations in our cohort (i.e., mother and daughter in three families and two siblings in four families) is similar to that reported in other studies. In Corbett's study, there were seven families with a parent and child relationship and four families with a 2-sibling combination. We consider that the higher incidence within families, type of family relations, and absence of other contributing risk factors (except for an increased BMI) implies the possibility of a genetic factor in this subgroup of patients.

Notably, patients within families also seem to have a similar course and similar response to treatment. These findings may imply that family relatives tend have a similar IIH course, independent of other contributing risk factors, and thus are further suggestive of a genetic source for IIH. We do not believe that environmental factors play a significant role in those cases specifically because the families were from different cities throughout Israel and because, although some family members lived together during the development of IIH symptoms, they developed IIH at different time periods and not simultaneously.

One major advantage of this report, compared to earlier ones, is that the vast majority of the patients, although not necessary diagnosed in our center, were physically examined in our clinic, and the original clinical reports (magnetic resonance imaging reports and lumbar puncture results) were reviewed by us. The three exceptions included one patient who was not examined in our clinic but for whom we had obtained all of her medical records through her relative, with her consent, and two patients who were only reported by their relative (the index patient) and we did not have access to the original clinical data.

We emphasize that IIH is generally underdiagnosed. It has highly variable clinical presentation and some patients have no symptoms at all and are diagnosed incidentally, while others complain of transient visual obscurations or tinnitus and are misdiagnosed since they have no headache. As Corbett [14] had reported, 11% of the patients in his cohort were asymptomatic and IIH was only diagnosed after papilledema was incidentally found during a routine eye examination. Unless physicians are looking for these signs, affected individuals and their family members may remain unidentified as having IIH.

The main limitations of our report are that it is a retrospective case series and that some patients were diagnosed in a remote geographic place or time. Although family neurological and ophthalmological history is integral to the information elicited during the medical history questioning of every patient that attends our clinic, we did not use a questionnaire specifically designed for this study, but rather based our information only on a retrospective review of medical records. As such, we propose that the actual number of familial IIH cases in our clinic may be underestimated.

CONCLUSIONS

This current patient cohort, which represents the heterogeneous Israel population (our neuro-ophthalmic division is part of a central tertiary referral center serving patients nationwide), had characteristics similar to those found by Corbett [14] in Jackson, Mississippi, USA. Our findings further support the conclusions reached in both reports, that the incidence of familial IIH cases is apparently much more common that had been previously estimated. Still, having found an incidence of 2.9%, we do not believe that routine evaluation of first-degree relatives of patients with IIH can be justified. It does, however, emphasize the importance of patient education and general physician awareness for the signs and symptoms of this pathology, especially among obese family members of diagnosed IIH patients. We believe that further genetic evaluation of these familial cases may yield useful information about the pathogenesis and the genetic bases of this disorder.

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Correspondence

Dr. A. Klein

Dept. of Ophthalmology, Tel Aviv Sourasky Medical Center, Tel Aviv 6423906, Israel

Phone: (972-3) 697-3048

Fax: (972-3) 697-3867

email: euriya@gmail.com

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Capsule

IgG3 regulates tissue-like memory B cells in HIV-infected individuals

Immunoglobulin G3 (IgG3) plays an uncertain role in the response to infection with and vaccination against human immunodeficiency virus (HIV). **Kardava** and collaborators described a regulatory role for IgG3 in dampening the immune system-activating effects of chronic HIV viremia on B cells. Secreted IgG3 was bound to IgM-expressing B cells in vivo in HIV-infected chronically viremic individuals but not in early-viremic or aviremic individuals. Tissue-like memory (TLM) B cells, a population expanded by persistent HIV viremia, bound large amounts of IgG3. IgG3 induced clustering of B cell antigen receptors (BCRs) on the IgM+ B cells, which was mediated by direct interactions between soluble IgG3 and membrane IgM of the BCR (IgM-BCR). The inhibitory IgG receptor CD32b (FcγRIIb), complement component C1q and inflammatory biomarker CRP contributed to the binding of secreted IgG3 onto IgM-expressing B cells of HIV-infected individuals. Notably, IgG3-bound TLM B cells were refractory to IgM-BCR stimulation, thus demonstrating that IgG3 can regulate B cells during chronic activation of the immune system.

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Eitan Israeli

Capsule

Modulation of inflammatory arthritis in mice by gut microbiota through mucosal inflammation and autoantibody generation

Observations of microbial dysbiosis in patients with rheumatoid arthritis (RA) have raised interest in studying microbial–mucosal interactions as a potential trigger of RA. Using the murine collagen-induced arthritis (CIA) model, **Jubair** et al. undertook this study to test our hypothesis that microbiota modulate immune responses leading to autoimmune arthritis. CIA was induced by immunization of mice with type II collagen (CII) in adjuvant on days 0 and 21, with arthritis appearing on days 23 and 24. Intestinal microbiota were profiled by 16S ribosomal RNA sequencing every 7 days during the course of CIA, and intestinal mucosal changes were evaluated on days 14 and 35. Then, microbiota were depleted either early (7 days before immunization) or late (day 21 after immunization) by administration of broad-spectrum antibiotics. Disease severity, autoantibody and systemic cytokine production, and intestinal mucosal responses were monitored in the setting of microbial reduction. Significant dysbiosis and mucosal inflammation occurred early in CIA, prior to visible arthritis, and continued to evolve during the course of disease. Depletion of the microbiota prior to the induction of CIA resulted in approximately 40% reduction in disease severity and in significantly reduced levels of serum inflammatory cytokines and anti-CII antibodies. In intestinal tissue, production of interleukin-17A (IL-17A) and IL-22 was delayed. Unexpectedly, microbial depletion during the late phase of CIA resulted in a › 50% decrease in disease severity. Anti-CII antibodies were mildly reduced but were significantly impaired in their ability to activate complement, likely due to altered glycosylation profiles. These data support a model in which intestinal dysbiosis triggers mucosal immune responses that stimulate T and B cells that are key for the development of inflammatory arthritis.

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Eitan Israeli