

Familial Idiopathic Intracranial Hypertension

Ksenija Karaman, Antonela Gverović-Antunica¹, Igor Žuljan, Nenad Vukojević², Boris Zoltner³, Ivana Erceg⁴, Ante Ivkošić⁴

Department of Ophthalmology, Split University Hospital Center and School of Medicine, Split; ¹Department of Ophthalmology, General Hospital Dubrovnik, Dubrovnik; ²Department of Ophthalmology, Zagreb University Hospital Center and School of Medicine, Zagreb; ³Department of Radiology, and ⁴Laboratory for Clinical and Forensic Genetics, Split University Hospital Center, Split, Croatia

Aim. To analyze the development and occurrence of the idiopathic intracranial hypertension and consequent visual loss in a family affected with idiopathic intracranial hypertension.

Methods. We studied 15 members of the same family and found six of them affected with idiopathic intracranial hypertension, which was accompanied with visual loss as a repercussion of the disease. Idiopathic intracranial hypertension was diagnosed on neurological and radiological examination. Visual examination to establish visual loss included fundoscopy, visual acuity, visual field testing, and ultrasonography of the optic nerve.

Results. The construction of a family tree and detailed examination of 15 family members revealed idiopathic intracranial hypertension with visual disturbances, even amaurosis, and different stages of visual field constriction in three members of the family: the mother and her two daughters. Due to the symptoms of idiopathic intracranial hypertension, such as headaches, nausea, vertigo, and the presence of transient visual obscuration and papilledema, in three other members of this family (aged 16, 17, and 25 years), we considered a presumptive diagnosis of idiopathic intracranial hypertension, and the need for thorough follow-up. Medical data on the family grandmother, who died 34 years ago, suggested that she also had symptoms of idiopathic intracranial hypertension. One of the patients underwent surgical treatment by a lumbo-peritoneal shunt operation worsening of the symptoms.

Conclusion. It is very important to include idiopathic intracranial hypertension in differential diagnosis of papilledema and recognize it in early stages to prevent vision loss. Current successful therapeutic approaches and close follow-up of such patients require teamwork of neurologists, ophthalmologists, and neurosurgeons.

Key words: *empty sella syndrome; genetic predisposition to disease; intracranial hypertension; papilledema*

Idiopathic intracranial hypertension was initially described by Quincke, and first named "pseudotumor cerebri" by Nonne (1). In 1955, Foley introduced the term "benign intracranial hypertension," which then had to be abandoned because of the high incidence of visual loss (1). Idiopathic intracranial hypertension is a syndrome defined by an increased intracranial pressure of unknown etiology, which predominantly affects obese women of childbearing age or women with recent weight gain (1,2). Some authors reported asthma and radicular spinal and back pain as associated factors (3). Pathophysiology of idiopathic intracranial hypertension can be explained by disturbed production or absorption of cerebrospinal fluid through the arachnoid granulations (2). Idiopathic intracranial hypertension has to be diagnosed according to modified Dandy's criteria (4), which include signs and symptoms of increased intracranial pressure, includ-

ing papilledema; increased opening pressure on lumbar puncture with normal cerebrospinal fluid composition; normal neurological examination (except for the VI nerve palsy) in an alert and awake patient; and absence of ventriculomegaly or intracranial space-occupying lesions on neuroimaging studies. There are some reports of correlation between optic nerve sheath diameter and increased intracranial pressure (5,6). Optic nerve sheath diameter has a tendency to be much wider in patients with idiopathic intracranial hypertension than in healthy individuals. Although findings on magnetic resonance imaging (MRI) or computed tomography (CT) (except sometimes smaller or even larger ventricles that can be observed in idiopathic intracranial hypertension) are usually normal, the contributing factors to the diagnosis of idiopathic intracranial hypertension are subjective symptoms, such as headache, pulsatile tinnitus, diplopia,

vomiting, and intracranial noises (1,2). Symptoms of the visual system are unusual visual disturbances, such as flashes; transient visual obscuration, such as episodes of transient blurred or grayed vision usually lasting up to one minute; photophobia; metamorphopsia; and diminished color vision (1,2). Familial occurrence of the disease is very rare and occasionally has benign characteristics with few or no symptoms (3,7-16). On the other hand, idiopathic intracranial hypertension can lead to visual loss, even blindness. Incidence of idiopathic intracranial hypertension is 0.9 per 100,000 population, and between 19-25 per 100,000 obese women of childbearing age, with women to men ratio of 8:1 (1,18). According to our knowledge, only 12 case reports of a familial presentation of idiopathic intracranial hypertension have been reported so far (3,7-16). Some of them emphasized autosomal dominant, whereas others reported autosomal recessive transmission of the disease and postulated multifactorial causes and genetic mechanism of idiopathic intracranial hypertension (16,17). We present a family affected with idiopathic intracranial hypertension and manifest visual conditions. The family had more affected members than any other family reported so far.

Subjects and Methods

Ophthalmological examination was performed in 15 members of the family. Further investigation included six family members: three with confirmed and three with presumptive diagnosis

of idiopathic intracranial hypertension. All of them met Dandy's criteria (4), except that in cases 2, 4, 5, and 6, the pressure of the cerebrospinal fluid was not measured because the patients or their parents refused to undergo the examination. All patients were examined to exclude secondary background of idiopathic intracranial hypertension, such as different toxic associations (corticosteroids withdrawal, tetracycline and vitamin A use), menstrual irregularity, and other. There were no symptoms of idiopathic intracranial hypertension among non-consanguineous family members who had been living with the family for years and shared the same lifestyle. Also, there were no possible environmental factors, such as occupational exposure to some chemicals or living conditions that could cause such a disease presentation in this family. The diagnosis of empty sella syndrome and absence of space-occupying lesions was proved by neuroimaging examination, such as CT of the brain and orbits and brain MRI, which included hypophyseal gland, chiasma, and optic tract

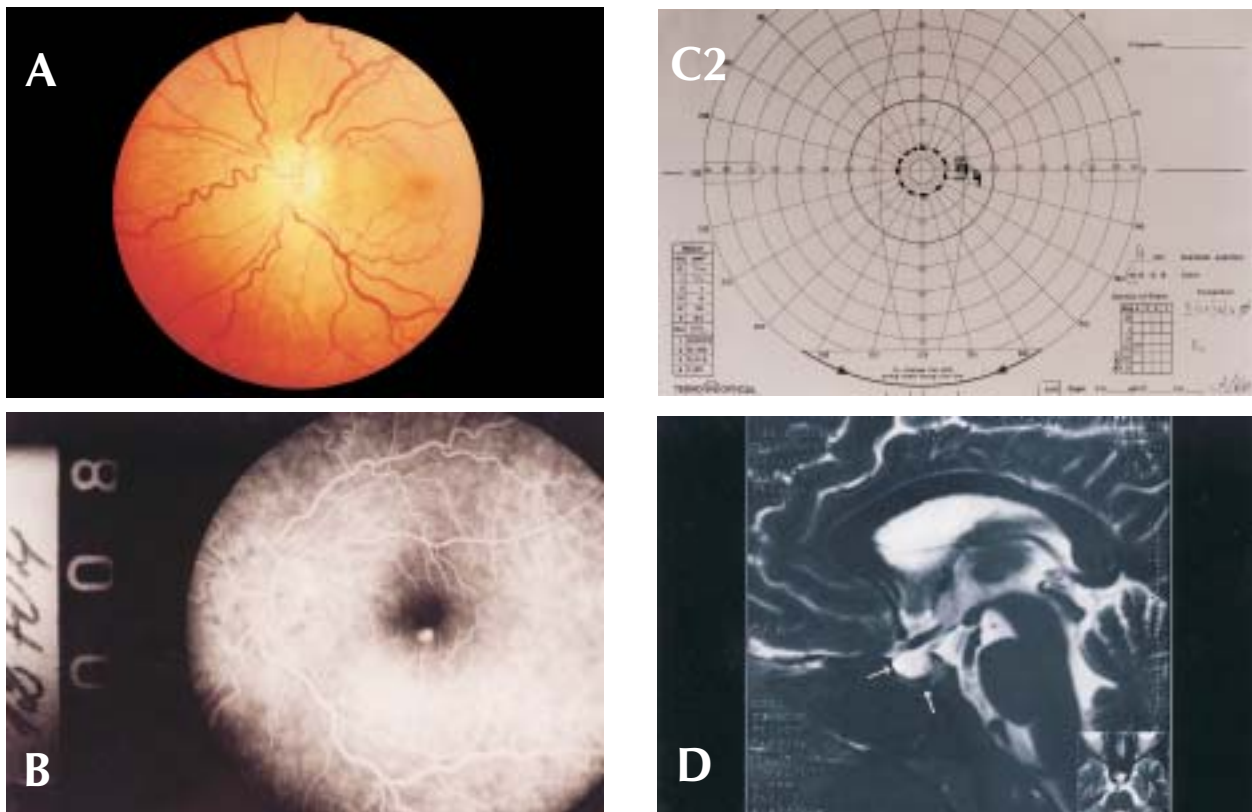


Figure 1. Clinical findings in Case 1. **A.** Chronic papilledema. **B.** Delay in fluorescein angiographic filling of the optic disc in chronic papilledema. **C.** Goldmann perimetry showing severe constriction of visual fields in both eyes. **C1** is the left eye, **C2** is the right eye. **D.** Empty sella. T2-weighted sagittal magnetic resonance image shows upper pituitary surface and posterior displacement of the pituitary infundibulum (right arrow); cerebrospinal fluid-filled arachnocele (left arrow).

scans. Neurological examination was performed to exclude other disorders known to cause increased intracranial pressure.

Visual Examination

Ultrasonographic examination of the eye included measurement of the optic nerve sheath diameter and intraocular protrusion of the optic nerve head. A commercially available scanner was used and a scan (A and B scan) was made from the position of 3 mm behind the papilla in axial transbulbar view. Normal values of the optic nerve sheath diameter are up to 4.1 mm (5). In case 1, ultrasonographic examination was repeated after the surgery. Ophthalmoscopic examination (direct, indirect, and by use of Goldman's lens) was performed at all visits and papilledema was graded from blurred disc (grade 1) to severe papilledema (grade 5), as proposed by Frisen (17). Goldmann perimetry was used to measure the visual field in all cases as well as in case 1 who underwent surgery, in whom the perimetry was performed several times during the six-month follow-up. Snellen charts were used for assessment of visual acuity in all cases. In case 1, fluorescein angiography was also performed.

Results

Case 1, a woman aged 35 years, was referred to the neurological department because of headache, vertigo, nausea, and radicular spinal and back pain during the previous few months. Medical examination excluded any cerebral space-occupying lesions and other possible causes of her condition. Considering all findings, idiopathic intracranial hypertension was established as the preliminary diagnosis. The patient was transferred to the Department of Ophthalmology because of progressive vision loss. Papilledema grade 5 and extreme constriction of visual fields in both eyes were established, together with other visual pathology (Figs. 1A, 1B, 1C1, and 1C2). MRI showed an empty sella (Fig. 1D), flattening of the posterior sclera, and distension of perioptic subarachnoid space. High cerebrospinal fluid pressure (500 mm H₂O), with normal composition of cerebrospinal fluid confirmed idiopathic intracranial hypertension as the final diagnosis. Her family history revealed the existence of similar symptoms in other family members, which indicated a potential familial presentation of this very rare disease. All members of this family were traced and the family tree was constructed (Fig. 2). Idiopathic intracranial hypertension with severe papilledema and empty sella syndrome were diagnosed in II/2, III/1, and III/2 (case 1), whereas different stages of papilledema and symptoms of increased intracranial pressure and idiopathic intracranial hypertension, respectively, were found in three other members of this family (III/7, III/8, and IV/1; Fig. 2). Cases 1 and 3 met all Dandy's criteria for the diagnosis of idiopathic intracranial hypertension. Although case 2 refused lumbar puncture, the final diagnosis of

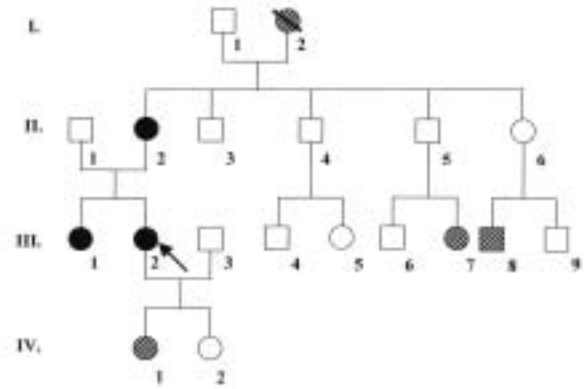


Figure 2. Family tree of the affected family. Case 1 – III/2 (proband); case 2 – III/1 (proband's sister); case 3 – II/2 (proband's mother); case 4 – IV/1 (proband's daughter); case 5 – III/7 (proband's cousin); and case 6 – III/8 (proband's cousin).

idiopathic intracranial hypertension was considered correct due to typical symptoms and findings. Three other members of the family had presumptive diagnosis of idiopathic intracranial hypertension, because they met all Dandy's criteria except for lumbar puncture. The reasons for the presumptive diagnosis were clinically suspicious symptoms of idiopathic intracranial hypertension, such as headache, vertigo, pulsatile tinnitus, photophobia, transient visual obscuration, findings of blurred disc borders or papilledema in each of them, and also the first grade of empty sella syndrome (case 6) according to Gibby et al (18). Some of the cases had obesity (cases 1, 2, and 5), asthma (case 3) or high blood pressure (cases 2 and 3) as accompanying factors of idiopathic intracranial hypertension (Table 1). The values of cerebrospinal fluid opening pressure measured in cases 1 and 3 were higher (500 and 450 mm H₂O, respectively) than the normal values of 200 mm H₂O (1,2). Optic nerve sheath diameter measurements revealed much higher values than normal (normal is up to 4.1 mm) in cases 1, 2, and 3, whereas the values were normal in cases 4, 5, and 6 (Table 2). There was no correlation between optic nerve sheath diameter and the stage of visual loss. Postoperative optic nerve sheath diameter in case 1 decreased to normal values after lumbo-peritoneal shunt surgery (3.3 mm right eye and 3.0 mm left eye), but visual acuity and visual field remained unchanged. Visual acuity was impaired in cases 1, 2, and 3, even to blindness in the left eye in case 2, but it was normal in cases 4, 5, and 6 (Table 1). Cases 1, 2, and 3 had an empty sella syndrome grade

Table 1. Clinical data of patients, all members of the same family, with idiopathic intracranial hypertension*

| Case [†] | Age (years) | Sex | Symptoms | | | Visual acuity | | |
|-------------------|-------------|-----|----------|--------------|------------------|---------------|-----------|------------------------------------|
| | | | ocular | neurological | duration (years) | right | left | CSF pressure (mm H ₂ O) |
| 1 | 34 | F | TVO, VL | HA, VE, VO | 1 | 0.3 | 0.01 | 500 |
| 2 | 36 | F | VL | HA, VE, VO | 8 | 1.0 | amaurosis | R |
| 3 | 54 | F | VL | HA, VE | 23 | 0.5 | 0.5 | 450 |
| 4 | 16 | F | TVO | HA | 1 | 1.0 | 1.0 | R |
| 5 | 25 | F | TVO | HA | 10 | 1.0 | 1.0 | R |
| 6 | 17 | M | TVO, PH | HA | 1 | 1.0 | 1.0 | R |

*Abbreviations: CSF – cerebrospinal fluid; F – female; M – male; TVO – transient visual obscurations; VL – visual loss; PH – photophobia; HA – headache; VE – vertigo; VO – vomiting; R – refused.

[†]1 – proband; 2 – proband's sister; 3 – proband's mother; 4 – proband's daughter; 5, 6 – proband's cousins.

Table 2. Magnetic resonance imaging (MRI) and ultrasonographic (USO) findings in patients with idiopathic intracranial hypertension, all members of the same family

| Case No. | MRI | | | USO | | | |
|----------|-----------------|--------------------|---------------------|---------------------------|------|------------------------|---|
| | sellar content* | scleral flattening | vertical tortuosity | optic nerve diameter (mm) | | intraocular protrusion | |
| | | | | right | left | | |
| 1 | ES | + | - | 5.1 | 7.8 | + | + |
| 2 | ES | + | + | 5.7 | 6.8 | + | + |
| 3 | ES | - | - | 6.2 | 5.7 | + | + |
| 4 | N | - | - | 2.8 | 2.6 | - | - |
| 5 | N | - | - | 2.0 | 2.4 | - | - |
| 6 | ES | + | - | 3.3 | 3.5 | + | + |

*ES – empty sella, N – normal.

Table 3. Fundus ophthalmoscopic findings in patients with idiopathic intracranial hypertension, all members of the same family

| Case No. | Papilledema (grade 1-5) | | elevated | hyperemic | Papilla | | |
|----------|-------------------------|------|----------|-----------|---------|------------------------|-------------|
| | right | left | | | pale | tortuous blood vessels | hemorrhages |
| 1 | 5 | 5 | + | - | + | + | + |
| 2 | 5 | 5 | + | - | + | + | - |
| 3 | 5 | 5 | + | - | + | + | - |
| 4 | 1 | 2 | + | + | - | - | - |
| 5 | 1 | 2 | + | + | - | - | - |
| 6 | 3 | 3 | + | + | - | - | - |

3, which could be attributed to long-term idiopathic intracranial hypertension or congenital incomplete diaphragma sellae, and may have been a contributing factor in visual loss development. Other MRI findings were in accordance with idiopathic intracranial hypertension (Table 2). Ophthalmoscopic examinations of the fundus revealed a variety of papillary changes including hyperemic, blurred, and prominent optic discs, pale papillae, and tortuous blood vessels (Table 3). Visual field examinations revealed a larger blind spot in all cases in both eyes together with different stages of visual field constriction.

Discussion

Idiopathic intracranial hypertension occurs predominantly in obese women of childbearing age or in women with recent weight gain, and its familial presentation is very rare (1,2). Many toxic factors may trigger the development of this disease, and the list of these noxious agents is expanding (2). We noticed that five of our patients had been treated several times with penicillin and macrolide antibiotics due to respiratory tract infections, so there is a possibility that these agents could have been the trigger for the disease. If this observation is true, these patients may have an underlying genetic susceptibility as a predisposing factor for the development of intracranial hypertension. Empty sella syndrome often accompanies idiopathic intracranial hypertension and occurs because of prolonged increased intracranial pressure or congenital incomplete or absent diaphragma sellae, which leads to the herniation of the subarachnoid cistern into the sella turcica. Cases 1, 2, and 3 had empty sella syndrome grade 3, whereas case 6 had grade 1 of empty sella or partially empty sella on MRI. In this patient, fully developed empty sella syndrome might be expected in the future. Empty sella syndrome correlates with idiopathic intracranial hypertension in 10-46%, even up to 90% of the cases (18-21). Although it was reported that empty sella syndrome can lead to partial pituitary deficiency (22), this was not

observed in our patients. Increased intracranial pressure can cause papilledema, or optic disc swelling, produced by the cessation of axoplasmic transport through the axon, which leads to the accumulation of axonal contents in the nerve fiber layer, thus elevating the optic nerve head (2). There was no correlation between the duration of idiopathic intracranial hypertension and progression of visual loss in our patients. Case 3 had idiopathic intracranial hypertension for more than 23 years and had the smallest vision loss. According to her medical data and our examination, her visual condition remained unchanged for years, suggesting a benign course of the disease. On the other hand, cases 1 and 2 had a rapid progression of visual loss after only one and eight years of duration of disease, respectively. Interestingly, their grandmother, who died in 1968, was probably an idiopathic intracranial hypertension patient according to her medical data. She had the diagnosis of papilla stagnans, distinctive symptoms of increased intracranial pressure, with high opening pressure on lumbar puncture, and normal findings of cerebrospinal fluid composition. Such a profound presentation in the family tree has not previously been reported. Cases 4, 5, and 6 met all Dandy's criteria for diagnosis except the measuring of cerebrospinal fluid pressure, which was postponed because of their refusal, their mild symptoms, and normal findings of optic nerve sheath diameter measurements. We established presumptive diagnosis, even though our findings showed that the full development of idiopathic intracranial hypertension might be expected later on in their lives. Idiopathic intracranial hypertension sometimes has benign characteristics and vision loss may not occur. However, asymptomatic patients still need a thorough clinical follow-up, even though the diagnosis is only provisional and parents have to be made aware of the potential risk of avoiding lumbar puncture. Vision loss in idiopathic intracranial hypertension may be caused by two mechanisms: ischemic and mechanical. Ischemia leads to the worsening of visual acuity, which correlates with greater impairment of

retrobulbar circulation (23). The second potential mechanism in empty sella syndrome is when mechanical traction of the optic chiasm by arachnoidal diverticulum pulls optic nerves against the anterior rim of the sella (24). This dislocation can cause compression on the circle of Willis, and subsequent ischemia. Medical treatment of the disease includes a therapeutic regimen of acetazolamide, furosemide, corticosteroids, and weight loss. Surgical treatment includes optic nerve sheath fenestration by using a medial orbitotomy operative approach and lumbo-peritoneal shunt, which is indicated in cases of worsening headache that failed to respond to medical therapy (1,2,25). Case 1 was surgically treated by lumbo-peritoneal shunt and values of her optic nerve sheath diameter became normal, but visual acuity and visual field failed to improve after surgery, which may be explained by irreversible changes and atrophy of the optic nerves. There is scarce knowledge of the genetic aspects of idiopathic intracranial hypertension. Some reports discuss possible genetic transmission of idiopathic intracranial hypertension; this presumption relies on familial occurrence of idiopathic intracranial hypertension in successive generations, which suggests autosomal dominant and, in siblings, recessive transmission (14). In the family we described, some of the patients had signs of the disease even though their parents were healthy, which suggests a different penetration and expression of the genes responsible for idiopathic intracranial hypertension among the family members. Further research in genetic aspects of idiopathic intracranial hypertension is needed in the future.

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Correspondence to:

Ksenija Karaman
Department of Ophthalmology
Split University Hospital
Spinčićeva 1
21000 Split, Croatia
ksenija.karaman@kbsplit.hr