

## Idiopathic Intracranial Hypertension: Etiological factors, Clinical Features, and Prognosis

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### ABSTRACT

**Introduction:** Idiopathic intracranial hypertension (IIH) occurs due to increased intracranial pressure (ICP), is most commonly encountered in obese women, and may lead to loss of vision. This study aimed to determine the demographic features, clinical signs and symptoms, and radiological findings of patients with IIH, and to investigate the factors associated with the prognosis.

**Methods:** Patients with IIH who were examined and followed-up between January 1992-January 2012 in the Neuro-ophthalmology Unit were retrospectively evaluated. Patients were diagnosed based on the modified Dandy criteria.

**Results:** The mean age of 59 patients included in the study (female, 88.1%) was 30.25±13.12 years. Reported complaints were headache (78.0%), transient visual obscuration (45.8%), nausea (32.2%), dizziness (16.9%), and diplopia (13.6%). Of the patients 69.4% had visual field deficits, and 71% had papilledema (66.1% were bilateral). The rate of

obesity was 20.3%. The prognosis was good in 64.7% of the patients, and 35.3% of the patients clinically worsened. Recurrence of symptoms was observed in 33% of the patients and 4 patients had severe permanent vision loss. Demographic features, initial complaints, mean ICP, and pathological magnetic resonance imaging findings were not associated with the prognosis. Delay in treatment and generalized constriction in the visual field were associated with the poor prognosis.

**Conclusion:** Compared to patients with IIH in the western population, obesity was less frequent in the present study. Initial visual field defects, especially the generalized constriction and delay to treatment were related to poor prognosis. Cessation of medical treatment was a factor for recurrence. Early diagnosis and appropriate treatment may subside the severity of permanent vision loss in fulminant IIH.

**Keywords:** Intracranial hypertension, pseudotumor cerebri, headache, obesity

**Cite this article as:** Keskin AO, İdman F, Kaya D, Bircan B. Idiopathic Intracranial Hypertension: Etiological factors, Clinical Features, and Prognosis. Arch Neuropsychiatry 2020;57:23-26.

### INTRODUCTION

Idiopathic intracranial hypertension (IIH), commonly called as pseudotumor cerebri, is a disorder that occurs due to increased intracranial pressure (ICP), the cause of which is not known. IIH is most commonly encountered in obese women of childbearing age (1) and its incidence is 1 to 2 per 100,000 (2). The modified Dandy criteria are used in the diagnosis of IIH.

The pathogenesis of IIH is unknown; the proposed hypothesis includes cerebral venous outflow abnormalities, increased cerebrospinal fluid (CSF) outflow resistance, obesity-related increased abdominal and intracranial venous pressure, altered sodium and water retention mechanisms, and vitamin A metabolism abnormalities (3). The described risk factors for IIH are female gender, overweight, medication use, and systemic illnesses. However, most patients with IIH do not have any of these factors (4).

Symptoms of IIH include severe headache, transient visual obscuration (TVO), blurred vision, diplopia, pulsatile tinnitus, photopsia, retrobulbar pain, and dizziness (5). Among these, the most common symptom of IIH

is headache. Similar to all headaches, headache related to elevated ICP may worsen upon awakening and increase with the Valsalva maneuver. The most common signs associated with IIH are papilledema, visual field loss, and sixth nerve palsy. Papilledema is typically bilateral and symmetric, whereas it may also be asymmetric or unilateral. Secondary intracranial hypertension related to cerebral venous thrombosis can have quite similar clinical presentations with IIH.

To the best of our knowledge, there is no prospective series that have described the natural history of IIH in the literature. It is known that IIH is a long-term disease, which lasts months to years (6–8). Symptoms of IIH generally worsen slowly; however, a subset has a more fulminant course. Generally, a gradual improvement or stabilization is achieved by treatment. However, many patients have persistent papilledema, elevated ICP, and residual visual field deficits (4). Mainly visual fields are affected, while visual acuity and color vision are relatively spared (9, 10). Visual loss may be insidious until irreversible damage occurs (5). Therefore, early diagnosis and treatment can modify this disability. In the present study, it was aimed to determine demographic features, clinical

signs and symptoms, and radiological findings of patients with IIH and to investigate the initial factors associated with the prognosis.

## METHODS

Patients with IIH who were examined and followed-up from January 1992 through January 2012 in the Neuro-ophthalmology Unit of Neurology Department of Dokuz Eylül University were retrospectively evaluated. All patients fulfilled the modified Dandy criteria, and had no evidence of cerebral venous sinus thrombosis on routine computed tomography (CT) or magnetic resonance (MR) venography. Patients having other remarkable medical, psychiatric, or ocular disorders were excluded.

All patients were evaluated by an experienced neuro-ophthalmologist and underwent a complete general, neurological, and ophthalmologic examination including Snellen visual acuity, ophthalmoscopy, and perimetry. Papilloedema was documented and photographs of both optic discs were taken with pupils dilated. Symptoms, duration of symptoms prior to diagnosis, duration of follow-up periods, associated factors, neuro-ophthalmologic and neuroimaging findings, CSF opening pressure, medical and surgical treatments, and visual outcomes were obtained. Obesity was defined as body mass index  $\geq 30$  kg/m<sup>2</sup>.

Visual acuity, visual field (kinetic or automatic), and funduscopy examination findings were systematically reviewed. Neuroimaging tests were evaluated at the time of diagnosis. When there was a doubt regarding possible cerebral venous thrombosis, MR venography or CT venography was obtained. The patients, who could not have an MRI, had a head CT with contrast.

Factors associated with the prognosis of IIH were also investigated. Comparing to the baseline findings of patients, if clinical outcomes were stable and improved, they were considered to be associated with good prognosis; however, if clinical outcomes were poor and if there was a severe vision loss (visual acuity  $\leq 0.1$ ), they were considered to be associated with poor prognosis.

### Statistical Analyses

Statistical analyses were performed using the SPSS for Windows, version 15.0 (SPSS Inc., Chicago, IL, USA). Chi-square test, Fisher's Exact test, and Mann-Whitney U test were used for statistical analysis. A p value  $< 0.05$  was considered statistically significant.

## RESULTS

In the present study, 59 IIH patients with a mean age of  $30.25 \pm 13.12$  years (range, 18–54 years) were included. Of the patients, 52 were female (88.1%) and 7 were male (11.9%). At baseline, the mean duration of the complaints of the patients was  $23.7 \pm 32.4$  months (range, 4 days–10 years). Obesity (20.3%) was the most common risk factor, followed by diabetes/thyroidopathy (18.6%), menstrual abnormalities (8.5%), and oral contraceptive use (5.1%) (Table 1).

The mean CSF opening pressure was  $308.7 \pm 100.2$  mm H<sub>2</sub>O (range, 200–840 mm H<sub>2</sub>O). There was no significant difference between male and female patients in terms of CSF opening pressure ( $302 \pm 55$  mm H<sub>2</sub>O and  $319 \pm 54$  mm H<sub>2</sub>O, respectively;  $p = 0.585$ ). (Independent sample T test).

At presentation, the most common symptom was headache (78.0%), followed by TVO (45.8%), nausea (32.2%), dizziness (16.9%), diplopia (13.6%), and tinnitus (8.5%) (Table 2). Visual acuity was disturbed in 35 patients (59.3%). Perimetric examination revealed abnormal results in 41 patients (69.4%) and bilateral generalized constriction and enlarged blind spot were the most commonly observed visual field deficits (Table 3).

On funduscopy examination, papilloedema was observed in 71.2% of the patients, of whom 66.1% were bilateral. Optic atrophy was observed in 10 patients (Table 3). Of 59 patients, 38 (64.4%) had normal eye movement and 21 (35.6%) had eye movement disorder, most of which were due to sixth nerve palsy ( $n = 9$ , 15.3%).

Of the patients, 35 underwent MRI examination and 24 underwent head CT with contrast. Empty sella syndrome (15.3%) and transverse sinus stenosis (15.3%) were the most commonly observed pathological neuroradiological findings.

In the present study, 32 patients (54.2%) were treated only with acetazolamide, 11 patients were treated only with topiramate, and 11 patients (18.6%) were treated with both acetazolamide and topiramate. Optic nerve sheath fenestration was performed in 4 patients (6.8%) since they continued to deteriorate despite medical treatment or showed rapid disease progression. Lumboperitoneal shunts were placed in 2 patients (3.4%) with severe vision loss and disabling headache (Table 4).

The mean follow-up period was 14.4 months (range, 1–54 months) and 24 of 59 patients were on follow-up during the study. The prognosis was good in 64% of the patients and 35.3% of the patients had a poor prognosis. Recurrence of symptoms was observed in 33% of the patients and cessation of medical treatment was found to be related to the recurrence in 5 patients (14%). Four patients had severe permanent vision loss; all of them had generalized constriction of the visual field and their visual acuities were 0.1 or worse. Two of these patients had bilateral optic atrophy on funduscopy examination.

Demographic features, initial complaints, mean ICP, and pathological magnetic resonance imaging findings were not associated with the prognosis ( $p > 0.05$ ). Delay in treatment ( $p = 0.009$ ) and generalized constriction in the visual field ( $p = 0.02$ ) were associated with the poor prognosis (Table 5).

## DISCUSSION

Many questions have been remained unanswered about IIH. Its association with female gender and obesity is striking in western

**Table 1.** Factors associated with idiopathic intracranial hypertension

Factors	n (%)
Obesity	12 (20.3)
Diabetes/thyroidopathy	11 (18.6)
Menstrual abnormalities	5 (8.5)
Oral contraceptive use	3 (5.1)
Vasculitis (Neurobehçet's syndrome)	1 (1.7)

**Table 2.** Frequency of symptoms at presentation

Symptom	n (%)
Headache	46 (78.0)
Transient visual obscuration	27 (45.8)
Nausea	19 (32.2)
Dizziness	10 (16.9)
Diplopia	8 (13.6)
Tinnitus	5 (8.5)
Retrobulbar pain	4 (6.8)

**Table 3.** Visual field deficits and funduscopic findings of the patients

Signs	n (%)
Funduscopic evaluation	
Bilateral papilledema	39 (66.1)
Unilateral papilledema	3 (5.1)
Bilateral optic atrophy	7 (11.9)
Unilateral optic atrophy	3 (5.1)
Normal fundus	7 (11.9)
Visual fields	
Normal	18 (30.5)
Blind spot enlargement	
Unilateral	6 (10.2)
Bilateral	5 (8.5)
Generalized constriction	
Unilateral	4 (6.8)
Bilateral	15 (25.4)
Arcuate inferior field loss	4 (6.8)
Central scotoma & peripheral rim constriction	2 (3.4)
Blind spot enlargement unilateral & peripheral rim constriction unilateral	2 (3.4)
Could not be performed	3 (5.1)
Not recorded	1 (2.6)

**Table 4.** Medical and surgical treatments applied to the patients

Treatment	n (%)
Acetazolamide	32 (54.2)
Topiramate	11 (18.6)
Acetazolamide+topiramate	11 (18.6)
Optic nerve sheath fenestration	4 (6.8)
Fenestration + Lumboperitoneal shunting	2 (3.4)

countries. However, studies have indicated that IIH can also occur in males, non-obese adults, older adults, and in pre-pubertal children (3). It has also been reported that obesity is less frequent in Asians with IIH (11, 12). Among the 59 patients included in the present study, 12 (20.3%) were obese. Celebisoy et al. reported 30% of IIH patients were obese in the western part of Turkey (6). Compared to patients with IIH in the western population, obesity is less common in Turkish and Asian populations. Thus, pathogenesis of IIH may differ not only according to gender but also according to race.

In a study by Wall and George, the most common symptoms of IIH were reported as headache (92%) and TVOs (72%) (13). In another study, it was reported that TVOs were not correlated with the degree of ICP elevation and not predictive of future visual loss (14). In the present study, no associations were found between the initial symptoms and prognosis of IIH.

In patients with IIH, diplopia related to unilateral or bilateral sixth cranial nerve palsy due to increased ICP may be reported. However, diplopia may also occur due to oculomotor and trochlear nerve palsy (15, 16).

The frequency of optic atrophy and visual disability in the present study was higher than those reported in the literature (5, 13). It could be attributed

**Table 5.** Associations with prognosis

No associations with prognosis	Associated with poor prognosis
Demographic features	Duration of time before onset of the treatment (p=0.009)
Initial complaints	
Mean ICP	Initial visual field defects (generalized constriction) (p=0.02)
Pathological MRI findings	
Neuro-ophthalmological findings except visual field defects (p>0.05)	

ICP, intracranial pressure; MRI, magnetic resonance imaging.

to the longer mean duration of the symptoms ( $23.7\pm 22.4$  months) of the patients at the initial presentation to our unit. Therefore, delay in treatment was found to be a poor prognostic factor in the present study.

In order to determine the severity of optic nerve involvement and to follow-up the response to treatment, visual field testing is necessary in IIH. Visual field abnormalities in IIH are common and occur in approximately 50% of patients (17). The most common findings on perimetry are enlarged blind spot, generalized constriction, and inferonasal vision loss (7, 10). Generalized constriction indicates severe loss of the nerve fiber layer; however, this is a non-specific sign and may be seen with other abnormalities (18). In the present study, generalized constriction observed at presentation was associated with the poor prognosis and there were no other relevant factors that could lead to generalized constriction. Hence, we concluded that generalized constriction was a poor predictor of outcome.

It is reasonable to consider an association between visual function and ICP. In the literature, higher levels of ICP were reported to be correlated with poor visual outcome (19). However, there may also be no such a relationship because ICP is known to fluctuate considerably. In the present study as well, there was no relationship between the prognosis and high levels of ICP.

The frequency of radiological abnormalities observed in the present study was lower than those reported in the literature (20). However, those high rates may have been due to more detailed radiological evaluations carried out in the recent years. The present study depended on 20 years old experience and 24 patients were examined only with CT. Therefore, not clearly identified radiological abnormalities-especially from the first ten years of this study-might have been unnoticed.

In an open-label study, Celebisoy et al. (21) reported that topiramate appeared to be effective but without a significant difference compared with acetazolamide in the treatment of IIH. Generally, acetazolamide is used as the first step of medical treatment in our unit and topiramate is usually added for obese patients. In the present study, patients were treated with acetazolamide and/or topiramate. For fulminant IIH, optic nerve sheath fenestration is preferred at first and if the fenestration fails, lumboperitoneal shunting is performed. In the present study, optic nerve sheath fenestration was performed in four patients since they continued to deteriorate despite medical therapy or showed rapid disease progression. Two of them, who had bilateral severe generalized constriction, deteriorated despite fenestration. Lumboperitoneal shunts were placed in these two patients and they stabilized after surgery. Chandrasekaran et al. (22) reported that optic nerve sheath fenestration was effective in stabilizing or improving visual disability in the short to medium term and that the patients with severe visual field loss were stabilized following surgery. The prognosis for visual outcome is generally good in IIH. Clinic-based studies have reported the rate of severe visual loss as 6–14% (1).

In the present study, generalized constriction was the most important clinical finding which indicated poor prognosis and delay to treatment was also significantly associated with the poor prognosis. Sureda-Ramis and Alberca-Serrano tried to identify the risk factors related with a poor visual outcome in IIH (23). They indicated that atrophy of the disc, visual loss, and field defects (other than enlargement of the blind spot) were observed at the first examination and the presence of systemic hypertension was related with the poor prognosis.

In previous reports, it has been indicated that recurrence of the symptoms occurred in 8% to 38% of patients after recovery and that weight gain was related with the recurrence (24). Kesler et al. (24) investigated the long-term prognoses and visual outcomes of 54 patients with IIH and reported no recurrence while the patients were treated with acetazolamide. In the present study, cessation of medical treatment was related to the recurrence in five patients. In order to maintain treatment until stabilization, regular follow-up visits with serial examinations including visual acuity, formal visual field testing, and dilated fundus examination with optic disc photographs are recommended for such patients. Intervals for follow-up visits should be individualized based on the severity and response to treatment. If a patient has severe vision loss, follow-up visits can be scheduled at least once a month, even if the patient is clinically stable.

In conclusion, obesity was not frequent in the present study. Initial visual field defects, especially the generalized constriction and delay to treatment were related to poor prognosis. Cessation of medical treatment was a factor for recurrence. Early diagnosis and appropriate treatment may subside the severity of permanent vision loss in fulminant IIH. Therefore, IIH should be diagnosed immediately, treated appropriately, and followed-up regularly.

**Ethics Committee Approval:** Due to the fact that it is a retrospective study, approval of the ethics committee is not required.

**Peer-review:** Externally peer-reviewed.

**Author Contributions:** Concept - AOK, DK, Fİ; Design - AOK, DK, Fİ; Supervision - Fİ; Resource - AOK, DK, BB, Fİ; Materials - AOK, DK, BB, Fİ; Data Collection and/ or Processing - AOK, DK, BB, Fİ; Analysis and/or Interpretation - AOK, Fİ; Literature Search - AOK, DK, Fİ; Writing - AOK, Fİ; Critical Reviews - Fİ.

**Conflict of Interest:** No conflict of interest was declared by the authors.

**Financial Disclosure:** The authors declared that this study has received no financial support.

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