



## ARAŞTIRMA / RESEARCH

### Pseudotumor cerebri in children: etiology, clinical findings, prognosis

Çocuklarda psödötümör serebri: etyoloji, klinik bulgular, prognoz

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#### Abstract

**Purpose:** Clinical and neuroimaging findings, aetiologies, treatment modalities and durations, response to treatment, and neurological sequelae of the patients diagnosed with pseudotumor cerebri were reviewed.

**Materials and Methods:** A total of 27 patients who followed up in the Department of Pediatric Neurology at Çukurova Medical Faculty between June 2015 and May 2018 were included in this study. Age, gender distribution, anthropometric measurements, cerebrospinal fluid pressures, neurological, ophthalmologic, neuroimaging and neurological sequelae findings, treatment modalities and durations, response to therapy of 27 patients were reviewed retrospectively.

**Results:** Mean cerebrospinal fluid pressure was 43.2±9.1cmH<sub>2</sub>O. The most frequent cause in aetiology were obesity (33.3%), iron deficiency anemia (18.5%) and venous sinus thrombosis (14.8%). All patients were treated with acetazolamid, 59.3% patients received only acetazolamid and 25.9% of patients received combined therapy with acetazolamide and topiramate and 14.8% of patients received combined therapy with acetazolamide and steroids. Of the patients, 25 had excellent neurological and opthalmological outcome with medical treatment.

**Conclusion:** The most frequently-seen neurological sequelae in pseudotumor cerebri is permanent visual impairment This irreversible situation affects the whole life of child. Therefore it is quite important to think about the diagnosis of pseudotumor cerebri for the children with complaints of headache, visual impairment and diplopia, and to subject them to treatment quickly and properly.

**Keywords:** Idiopathic intracranial hypertension, papillae edema, headache, childhood

#### Öz

**Amaç:** Psödötümör serebri tanısı alan hastaların klinik ve nörogörüntüleme bulguları, etiyolojileri, tedavi şekilleri ve süreleri, tedaviye yanıtları ve nörolojik sekel varlıkları gözden geçirildi

**Gereç ve Yöntem:** Çalışmaya dahil edilen hastalar Haziran 2015 ile Mayıs 2018 arasında Çukurova Tıp Fakültesi Çocuk Nöroloji Bilim Dalında takip edildi. Yirmi yedi hastanın yaş, cinsiyet dağılımı, antropometrik ölçümleri, BOS basınçları, nörolojik, oftalmolojik, nörogörüntüleme, nörolojik sekel bulguları, tedavi modaliteleri ve süreleri, tedavi yanıtı retrospektif olarak incelendi.

**Bulgular:** BOS basıncı ortalaması 43,2±9,1cmH<sub>2</sub>O idi. Etiyolojide en sık neden obezite (%33,3), demir eksikliği anemisi (%18,5) ve venöz sinüs trombozu (%14,8) idi. Hastaların %59,3'üne yalnızca asetazolamid tedavisi verildi, %25,9'una topiramate eklendi, %14,8'ine steroid verildi. 25 hastanın nörolojik ve oftalmolojik bulgularında medikal tedavi ile tamamen düzelme görüldü.

**Sonuç:** Psödötümör serebri hastalığında en sık oluşan nörolojik sekel kalıcı görme kaybıdır. Bu durum geri dönüşümsüz olur ve çocuğun tüm hayatını etkiler. Bu nedenle baş ağrısı, görme kaybı, çift görme şikayetleri olan çocuklarda Psödötümör serebri tanısının düşünülmesi gerektiğinin bilinmesi ve çocukların hızlı ve uygun şekilde tedavisi prognozda oldukça önemlidir.

**Anahtar kelimeler:** İdiyopatik intrakraniyal hipertansiyon, papil ödem, baş ağrısı, çocukluk çağı

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## INTRODUCTION

The pseudotumor cerebri (PS) is a clinical syndrome that occurs when intracranial pressure increases for no obvious reasons, it is known as idiopathic intracranial hypertension as well<sup>1</sup>. It is clinically manifested by headache (84-92%), visual impairment (68-72%), diplopia (18-38), photophobia (48-54%), pulsatile tinnitus (52-60%), retrobulbar pain (44%) and nausea (52-60%)<sup>2</sup>. These symptoms, even as a cluster, are not specific for PS. A neuroimaging study is required in patients suspected as having increased intracranial pressure to exclude other causes of elevated intracranial pressure. Magnetic resonance imaging (MRI) with and without contrast and including postcontrast MR venography is the imaging study of choice. Although cause of the syndrome cannot be clarified exactly, increased cerebrospinal fluid (CSF) production, decreased CSF absorption, high intracranial venous pressure and increased intracranial blood volume are held responsible. Increased intracranial pressure is diagnosed and papillae edema generally accompanies when CSF pressure exceeds 25cmH<sub>2</sub>O<sup>2,3</sup>. In literature, the cases which are not associated with papillae edema were reported due to high CSF pressure. The incidence of the syndrome in pediatric patients was 0.63/100,000<sup>4</sup>. The prognosis seems to be better in children than in adults. Spontaneous remission may occur even following the diagnostic lumbar puncture. Even though its aetiology and pathogenesis have not been enlightened yet, endocrine and metabolic problems, obesity, several drugs, hypervitaminosis A and sinus thrombosis were reported<sup>5</sup>.

In this study, clinical and neuroimaging findings, aetiologies, treatment modalities and durations, treatment response and presence of neurological sequelae of the patients diagnosed with PS were discussed.

## MATERIALS AND METHODS

In this study, 27 cases with regular drug usage and follow-ups whose follow-up periods were at least six months and who met diagnosis criteria of PS were chosen from 41 patients who applied to Çukurova University Outpatient Department of Pediatric Neurology between June 2015 and May 2018. These cases were subjected to a review. Ethics committee approval was obtained for the study in the meeting of Çukurova University Medical Faculty Noninvasive

Clinical Research Ethics Committee on June 1, 2018. Besides, consent from the families of the patients were received. Age, anthropometric measurements (weight, height and body mass index), CSF pressures, neurological, ophthalmologic and neuroimaging findings, treatment modalities and durations, response to treatment, and the presence of neurological sequelae of the patients were reviewed. All of the patients had magnetic resonance imaging. Color vision, visual field and visual acuity were evaluated during the ophthalmologic examination. Retinal nerve fiber layer thickness analysis was performed with optic coherence tomography. Modified Dandy criteria were used for PS diagnosis. The patients who met all of the criteria were diagnosed with PS. a. Papillae edema, b. Normal findings of neurological examination-except cranial nerve abnormalities, c. Normal neuroimaging: Hydrocephalus, mass, structural lesion and abnormal meningeal involvement should not exist, d. Normal CSF analysis, e. High CSF opening pressure ( $\geq 250$  mmH<sub>2</sub>O) in lumbar puncture (LP) applied properly. Diagnosis of PS can be suggested in the absence of papillae edema or sixth cranial nerve palsy, but a final diagnosis cannot be established<sup>6,7</sup>. Patients who didn't meet modified Dandy criteria and followed-up at least 6 months were excluded from this study.

## Statistical analysis

All analyses were performed using IBM SPSS Statistics Version 20.0 statistical software package. Categorical variables were expressed as numbers and percentages, whereas continuous variables were summarized as mean and standard deviation and as median and minimum-maximum where appropriate (IBM Corp. Released 2011. IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp.).

## RESULTS

Eighteen (66.7%) and 9 (33.3%) of 27 patients were female and male patients, respectively. Mean age was 12.5 $\pm$ 3.2 (age range from 5 to 17 years). Of the cases, prepubertal and pubertal periods in patients were 14 (51.9%) and 13 (48.1%) respectively. Body mass index of 6 patients exceeded 30 kg/m<sup>2</sup> whereas BMI of 3 patients was higher than 25 kg/m<sup>2</sup>. Mean CSF pressure was 43.2 $\pm$ 9.1cmH<sub>2</sub>O (25-83cmH<sub>2</sub>O). Mean follow-up period was 12.7 $\pm$ 3.3 (6 months-3 years). Headache, diplopia, blurred vision, vomiting and seizure were observed in 14 (51.8%), six (22.2%),

four (14.8%), two (7.4%) and one (3.7%) of the patients as the initial symptom, respectively (Table 1). Six patients had sixth nerve palsy in neurological examination whereas one patient had ataxia and left hemiparesis. Clinical findings of the patient with ataxia and hemiparesis were not related to PS. They were sequellae. All of the patients were subjected to cranial MRG examination. Apart from 17 (63.0%) normal patients, three (11.1%), one (3.7%), three (11.1%) and three patients (11.1%) had cortical atrophy, pineal cyst, arachnoid cyst and transverse sinus hypoplasia, respectively (Table 2). In MR venography, sinus thrombosis was found in four patients whereas sinus hypoplasia was detected in three patients. As part of aetiology, obesity, sinus hypoplasia, iron deficiency anemia, sinus thrombosis, B12 deficiency anaemia, and iron deficiency anemia and B12 deficiency anaemia together were determined in nine (33.3%), three (11.1%), five (18.5%), four (14.8%), four (14.8%) and two patients (7.5%), respectively. The patients with sinus thrombosis were checked with respect to Homocysteine, Protein C, Protein S, antithrombin III, factor VIII, lipoprotein a level, FV leiden, MTHFR, Prothrombin20210A genes mutation and antiphospholipid antibody. Administration of folbiol started for two patients with high homocysteine level.

**Table 1. Clinical findings of the patients**

Variable	n	%
Headache	14	51.9
Diplopia	6	22.2
Blurred vision	4	14.8
Vomiting	2	7.4
Seizure	1	3.7
Total	27	100

**Table 2. Findings of magnetic resonance imaging**

MRG findings	n	%
Normal	17	63.0
Cortical atrophy	3	11.1
Pineal cyst	1	3.7
Arachnoid cyst	3	11.1
Transverse sinus hypoplasia	3	11.1
Total	27	100

**Treatment:** Sixteen (59.3%) of the patients, were received only acetazolamide with a maximum dose of 1500 milligram/day. Seven patients (25.9%) received combined therapy with topiramate (1-9mg/kg). Four patients started to take steroid (1mg/kg) as the third alternative. Nine patients needed LP repetitively. Mean recovery period was  $5.7 \pm 3.6$  months (4-13

months). Medical treatment was ended within at least 6 months after the improvement in clinical and ophthalmologic findings.

### Prognosis

Neurological and ophthalmologic findings obtained from 25 patients (92.6%) completely improved with medical treatment. On the other hand, atrophy and permanent visual defect developed in one patient while lumboperitoneal shunt was placed on another patient (Figure 1 and 2).



**Figure 1. Transverse sinus thrombosis in cerebral magnetic venography of the patient with optic atrophy**



**Figure 2. Abdominal radiograph and cerebral magnetic image of a patient with a lumboperitoneal shunt.**

## DISCUSSION

Pseudotumor cerebri is a rare condition that may develop due to numerous causes. Aetiological causes may vary based on countries. Despite well-defined symptoms and findings of this syndrome, its pathogenesis is still not known exactly. It is thought that increased resistance to CSF flow may be its pathogenesis<sup>8</sup>. Pediatric PS patients were evaluated in two categories: pubertal and prepubertal. Risk factors of the pubertal patients were found to be similar with those of the adult patients. It was stated that gender, age and pubertal condition are of significance in aetiology. Female/male ratio of prepubertal patients is equal. In general, secondary PS is observed in this group. Secondary causes need to be searched in detail with respect to males<sup>9,10</sup>. In our study, 66.6% and 33.4% of our patients were female and male, respectively. Mean age was  $12.5 \pm 3.2$  (age range from 5 to 17 years).

PS pathogenesis of children has not been clarified, yet. CSF dynamics, endocrine causes, gender and underlying prothrombotic abnormalities are considered to be important aetiology. Even though their mechanisms of action are still not known exactly, it is thought that increased formation of CSF led by one of the substances released from fat tissue, the mineralocorticoids, prothrombotic effect of oestrogen (venous sinus thrombosis and microthrombotic obstruction of arachnoid villi) and mineralocorticoid effect of progesterone may raise intracranial pressure<sup>8,10</sup>. It is reported that the secondary causes of PS are cerebral venous sinus abnormalities (cerebral venous sinus thrombosis, middle ear or mastoid infection and hypercoagulability), drug usage (several antibiotics such as tetracycline, steroid recession, hypervitaminosis A, isotretinoin and lithium) and several diseases (hypoparathyroidism, Addison's syndrome, sleep apnea syndrome, anemia and renal failure)<sup>10</sup>. Discontinuation of chronic steroid usage and the use of growth hormone are reported as the most common secondary causes of PS in pediatric patients<sup>8,10</sup>. PS incidence rises with the increase in obesity in the world. Obesity, venous sinus thrombosis and anemia were found as the most common aetiological causes of PS in this study. Obese patients received a combination of diet therapy together with the medical treatment.

Neuroimaging is used to exclude the secondary causes of increased intracranial pressure in

Pseudotumor Cerebri<sup>11</sup>. However, it has been stated in recent studies that some of the small changes such as empty sella, flattening of posterior globus, intraocular protrusion of optic nerve, optic nerve tortuosity, expansion of perioptic CSF space and stenosis in transverse sinus may be the indicators of PS. Empty sella is the most frequently-reported finding among PS patients<sup>12-14</sup>. All of our patients were subjected to MRG examination in this study. Apart from 17 (62.9%) normal patients, three (11.1%), three (11.1%), one (3.7%) and three patients (11.1%) had cortical atrophy, pineal cyst, arachnoid cyst and transverse sinus hypoplasia, respectively. The finding of empty sella developed chronically depending on the increase in intracranial pressure. We think that the absence of empty sella-related finding in our patients results from MR examination in early period. In MR venography, sinus thrombosis was found in four patients whereas sinus hypoplasia was detected in three patients. Evaluation of MR venography in patients with pseudotumor cerebri is required for diagnosis and proper treatment.

The most common complaint that makes PS patients search for a physician consultation is headache. It is seen in 85.5.-96.5% of pediatric patients<sup>2,3,15</sup>. Headache was localized in frontal region of 68% of the patients. In the study, 36%, 30% and 47% of the headache complaints were reported to be generalized, unilateral and ocular, respectively. Besides, it was specified that photophobia and phonophobia accompanied headache symptoms of the patients by 70% and 52%, respectively. Fifty percent of patients' complaints increase with routine physical activity<sup>16</sup>. In our study, the most common complaints for application were headache (51.8%), diplopia (22.2%) and blurred vision (7.4%). Nine (64.2 %) of the patients had localized headache in frontal region in line with literature. In particular, the headache that starts in the morning, increase with strains and are accompanied by findings of blurred vision should be taken into account. Papillae edema was not found in 18 % of the patients with intracranial hypertension<sup>17</sup>. Although papillae edema is usually bilateral, unilateral cases were rarely reported. In our study, four (14.8 %) of our patients had unilateral papillae edema. Optic coherence tomography (OCT) and thickness of retinal nerve fiber are associated with the degree of papillae edema and can be used to follow up the patient<sup>17,18</sup>. Presence of papillae edema is evaluated ophthalmologically during the examination of fundus. However, varying severity of papillae edema, anatomical variations and the reasons leading to false

papillae edema can make diagnosis and follow-up abit difficult. As part of our study, visual space test, optic coherence tomography, retinal nerve fiber layer thickness analysis as well as ophthalmologic examination were performed to diagnose and follow up the patients. Thus, response to treatment was evaluated through both partially-subjective procedures such as ophthalmologic examination, and objective procedures, dose adjustments of the drugs used were made.

The aim of the treatment is to eliminate the symptoms and complications such as visual impairment. It is important to make early diagnosis and suggest the proper treatment in order to prevent complications. Treatment protocol consists of medical procedures, evacuator LP and surgical procedures. Weight loss is absolutely recommended to obese patients<sup>19-21</sup>. First-line treatment is acetazolamide which contains carbonic anhydrase enzyme inhibitors and has not changed in years. It creates effect by reducing the production of cerebrospinal fluid by 6-57 %<sup>21,22</sup>. In recent years, topiramate has been in the foreground as second-line treatment and found much better than furosemide in the studies on its efficacy. In literature, there are various studies which assert that topiramate is more effective than acetazolamide as well<sup>22-25</sup>. Especially, it has bilateral effects by contributing to weight loss of obese patients. Even though steroid treatment is suggested in several studies in literature, it is reported that the treatment should be avoided due to its side effects and that it may cause PS as rebound after the discontinuation of steroid usage<sup>22</sup>. In our study, 16 patients (59.3%) were administered only acetazolamide with a maximum dose of 1500 milligram/day. Seven patients (25.9%) received combined therapy with topiramate. Four patients (14.8%) started to take steroid as the third alternative. One of our patients did not respond to medical treatment, so lumboperitoneal shunt was placed. In our study, it was found out when weight control was achieved, the number of side effects declined and the patients who did not respond to acetazolamide treatment recovered receiving topiramate therapy more quickly. Further studies with wider series are required to apply topiramate therapy to PS patients as the first alternative. In stubborn cases, furosemide, steroids and surgical treatments (such as optic nerve fenestration and lumboperitoneal shunt) can be applied<sup>25,26</sup>.

This study had several limitations. The distribution of

prepubertal and postpubertal samples for statistical comparison was insufficient; measurement of CSF pressure and ophthalmologic examination were not performed by the same person and both processes were conducted retrospectively in a limited time, therefore such variables could not be analyzed. Prospective studies with increased sample size are required to obtain more reliable results.

Etiology and physiopathology of PS children were not clarified exactly. This disease may result in the neurological deficits such as permanent visual impairment. The children who do not meet the diagnosis criteria of primary headache completely require detailed medical history and examination as well as further study. Focusing on diagnosis of PS and quick and appropriate treatment are of importance for prognosis. More comprehensive studies are needed to enlighten pathophysiology and determine the clinical and imaging criteria.

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