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Etiology and prognosis of childhood pseudotumor cerebri syndrome: A retrospective single center study from Turkey

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Abstract

Objective: This study aim to investigate children who were diagnosed with pseudotumor cerebri (PTC) from a tertiary hospital in Turkey. *Methods:* This was a retrospective study based on medical records of 16 children diagnosed with PTC. All patients were followed up in the Pediatric Neurology Department of Keçiören Training and Research Hospital, between 2017 and 2021. Clinical and laboratory features of patients were reviewed. *Results:* Among the 16 patients diagnosed with pseudotumor cerebri, 50% were girls and 50% boys. The mean age at the disease onset was 12± 3.8 years (range: 4-17 years). Eleven patients (68.8%) were in the pubertal period and, five (31.3%) of them were in pre-pubertal period. Five patients (31.3%) were diagnosed with primary and eleven (68.8%) patients with secondary PTC. Underlying etiologies were obesity (37.5%), sinusitis (37.5%), and systemic lupus erythematosus (6.3%). Laboratory findings revealed vitamin D deficiency (68.8%); vitamin B12 deficiency (25%), iron deficiency anemia (12.5%), and vitamin A deficiency (6.3%). The most common symptoms were headache (93.8%), nausea and vomiting (25%), blurred vision (18.8%), photophobia (18.8%). All patients had bilateral papilledema. Four children were asymptomatic with papilledema detected incidentally on routine eye examination. Nine patients received medical treatment. Acetazolamide was the most prescribed medication (56%). Only one patient with epilepsy had combined treatment with topiramate, acetazolamide and then lumboperitoneal shunt. All patients responded to treatment with full recovery.
Conclusion: PTC is not rare in children, most were pubertal, and a quarter were asymptomatic diagnosed in routine fundus examination.

Keywords: Pseudotumor cerebri; children; headache; papilledema; etiology; puberty

INTRODUCTION

Pseudotumor cerebri (PTC) is a condition characterized by elevated intracranial pressure without an intracranial mass, inflammation, vascular abnormality, hydrocephalus on radiological examination, or changes in level of consciousness.[1-5] PT affects 0.71 out of every 100,000 children.[6,7] It is a rare condition in infants, with an estimated prevalence of 0.17 to 1.32 per 100,000 children.[8,9] Between the ages of 12 and 15, the prevalence rises, and 60 percent of children who experience the condition are over the age of 10.[10-12]

Increased intracranial pressure with normal neuroimaging, normal cerebrospinal fluid microscopy and biochemistry, normal neurologic evaluation (except for sixth cranial nerve palsy, papilledema, and vision loss), and no known etiology are characteristic of PTC.[13] Obesity and weight gain are risk factors during puberty. Many asymptomatic children are diagnosed with PTC during a regular ophthalmologic examination.[14-16] There are only a few studies on PTC in children. Our aim was to report all cases of PTC who were followed up recently in our hospital's pediatric neurology clinic.

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METHODS

This was a retrospective study involving 16 patients aged between four and seventeen year of age and who had been diagnosed with PTC using Dandy *et al*.[17] updated by Friedman guidelines.[18] Patients were recruited from the Pediatric Neurology Department of University of Health and Science, Keçiören Training and Research Hospital between 2017 and 2021. The age, gender, puberty, clinical manifestations, etiology, ophthalmologic, systemic, neurologic examination, cranial magnetic resonance imaging (MRI) and magnetic resonance venography (MRV) findings, treatment and prognosis of each patient were examined retrospectively. Lumbar puncture (LP) results, cerebro-spinal fluid (CSF) pressure and biochemical analysis were obtained. According to previous reports, patients under the age of 11 were deemed pre-pubertal, while those over the age of 11 were labeled pubertal.[2,16] Tanner stage for puberty could not be determined as the study was retrospective. Those with a body mass index above the 95th percentile were considered obese. Inclusion criteria for the diagnosis of PTC was according to the Friedman guidelines. Patients who fulfilled all of the following diagnostic criteria were diagnosed as having definite PS: 1. Signs and symptoms of increased intracranial pressure; 2. Absence of localizing findings on neurologic examination; 3. Absence of deformity, displacement, or obstruction of the ventricular system and otherwise normal neurodiagnostic studies, except for evidence of increased CSF pressure (200 mm water); abnormal 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 should lead to another diagnosis; 4. Awake and alert; 5. No other cause of increased intracranial pressure present. For CSF opening pressure of 200–250 mm water required at least one of the following: Pulse synchronous tinnitus; VI cranial nerve palsy; Frisen grade II papilledema; Echography for drusen-negative and no other disc anomalies mimicking disc edema present; Magnetic resonance venography with lateral sinus collapse/stenosis preferably using auto-triggered elliptic centric-ordered technique; Partially empty sella on coronal or sagittal views and optic nerve sheaths with filled out CSF spaces next to the globe on T2-weighted axial scans.

SPSS 22.0 was used as a package program in analyzes. Descriptive statistics were used. Data (%) or summarized as mean. Chi-square test used in two-way tables to determine the relationship between categorical variables.

Approval was obtained from the Local Ethics Committee (24/08/2021-Protocol No: 2012 -KAEK-15/2347) and the Ministry of Health for this retrospective study.

RESULTS

The mean age of symptom onset was 12±3.8 years (min 4- max 17 years). Eleven patients (68.8%) were in the pubertal period and five (31.3%) in pre-pubertal period. Five patients (31.3%) were diagnosed with primary and eleven (68.8%) patients with secondary PTC. The etiologies found were: obesity (37.5%), sinusitis (37.5%), and SLE (6.3%). Vitamin D deficiency was seen in 68.8%; vitamin B12 deficiency in 25%, iron deficiency anemia (IRA) in 12.5%, and vitamin A deficiency in 6.3%. One patient had epilepsy.

The most common symptom was headache (93.8%). The headache was most frequently described as unilateral frontal location that persisted whole day. It was often described as pressure-like and throbbing. The onset of headaches was between two weeks and two months. The other symptoms were vomiting and nausea (25%), blurred vision (18.8%), photophobia (18.8%), diplopia (12.5%), hypertension (12.5%), vertigo (6.3%), tremor (6.3%) and facial numbness (6.3%) (Table1).

All patients had bilateral papilledema in the fundus examination. Four of our patients were incidentally diagnosed with papillary edema during routine ophthalmic examination as healthy child during follow-up; they had no other signs of PTC and no eye symptom. For the eye examination, two had grade 2 papilledema (PE), others had grade 1 PE. Nine of the patients received medical treatment. The cranial magnetic resonance imaging (MRI/ MRV) were all normal. The mean cerebrospinal fluid (CSF) opening pressure of the patients was 33.83 ± 1.20 cm H_2O (min 32-max 36 cm H_2O).

The most commonly used medication was acetazolamide as mono therapy in nine (56 %) patients and in combination with topiramate in one patient. This patient did not respond to medical treatment and lumboperitoneal shunt was performed. Seven patients (47%) did not receive any active treatment. The median time till clinical resolution was 5 months. The mean follow-up periods were 2 years. There was resolution in all the patients and all neurological and ophthalmological examinations were eventually normal.

Table 1: Demographic, etiologic and clinic characteristics of patients

Patient	Gender /Age*	First Visit Symptom	Etiyology	Cranial MRI/ MRV	CFS Opening Pressure(cm H2O)	Accompanying Findings	Treatment
1	F/16	Headache, hypertension	Obesity	Normal	35	Vitamin D deficiency	None
2	F/12	Headache	Sinusitis	Normal	33	Vitamin D deficiency	None
3	M/9	Headache, diplopia	Sinusitis	Normal	34	Vitamin D deficiency	None
4	M/12	Headache, photophobia, vomiting nausea	Idiopatic	Normal	33	Vitamin D, vitamin B12 deficiency	Acetozalamide
5	M/8	Vertigo, vomiting, nausea	Idiopatic	Normal	36	Vitamin D deficiency	Acetozalamide
6	F/17	Headache, blurred vision, diplopia	Sinusitis	Normal	35	Vitamin D deficiency, IDA	None
7	F/15	Headache, facial numbness	Obesity	Normal	33	Vitamin D, vitamin B12 deficiency, epilepsy	Acetozalamide, topiramate, lumboperitoneal shunt
8	M/4	Headache	Sinusitis	Normal	34	Vitamin A deficiency	Acetozalamide
9	F/17	Headache, blurred vision	Obesity, sinusitis	Normal	33	Vitamin B12 deficiency, IDA	Acetozalamide
10	F/8	Headache, photophobia, tremor	Idiopatic	Normal	34	Vitamin D deficiency	Acetozalamide
11	F/9	Headache, vomiting, nausea	Obesity, SLE	Normal	36	Vitamin D deficiency	Acetozalamide
12	M/11	Headache	Idiopatic	Normal	32	Vitamin D, vitamin B12 deficiency	None
13	F/12	Headache, vomiting, nausea	Idiopatic	Normal	34	None	Acetozalamide
14	M/11	Headache	Obesity	Normal	32	None	Acetozalamide
15	F/15	Headache	Obesity	Normal	34	Vitamin D deficiency	None
16	M/17	Headache, blurred vision, photophobia, hypertension	Sinusitis	Normal	34	None	None

*IDA: Iron deficiency anemia, SLE: Systemic lupus erythematous, cMRI: Cranial magnetic resonance imaging, cMRV: Cranial magnetic resonance venography

DISCUSSION

PTC is a rare disease that affects children and adolescents. PTC affect typically overweight women. The incidence in the pre-pubertal period ranges from 45-60%.[2,19,20] In our study, the mean age of the patients was 12±3.8 years (min 4- max 17 years) and 68.8% of them were in the pubertal period.

The frequency of secondary PTC in the literature is between 28-42% and is more common in childhood than adults.[6] The pathophysiology of secondary PTC is still not fully understood. The most common causes of secondary PTC are; obesity, drugs (vitamin A, tetracycline, lithium, growth hormone or corticosteroid therapy), vitamin D deficiency, hypercapnia (sleep apnea syndrome), endocrine diseases (Cushing's disease, hypo/hyperthyroidism, hyperparathyroidism, Addison disease), anemia, renal failure, Turner syndrome, Down syndrome and autoimmune diseases (SLE, Sjögren syndrome).[18,21] Five patients (31.3%) were diagnosed with primary and eleven (68.8%) patients with secondary PTC. Secondary PTC was more commonly seen in pubertal children and female gender in our study (Table 2).

Obesity was found to be the underlying cause in six (37.5%) of our patients. For the explanation of the relationship between obesity and PTC; first, excessive fat tissue in obese patients result in changes in gonadal hormones, growth hormone and mineralocorticoid pathway and increasing CSF production in the choroid plexus.[22] Increased intra thoracic and intra-abdominal pressures can result in decreased intracranial venous drainage, which can slow the absorption of CSF and lead to increased intracranial pressure. Another mechanism being the higher prevalence of obstructive sleep apnea with hypercapnia among patients with obesity.[22] Previous studies have found an obesity rate in the pubertal period to be 43-68% and in the pre-pubertal period 25%, with an increasing trend towards obesity with age.[20,23] Primary PTC is thought to be more frequent in younger children, the non-obese and males.[24-26] This is consistent with our patients with the results of our study.

The relationship between infections and PTC has been reported in various studies. Ear infections and other diseases, such as sinusitis;

Table 2: Comparison of demographic and clinical features according to pseudotumor cerebri etiology

	Primary pseudo-tumor cerebri (n=5)	Secondary pseudotumor cerebri (n=11)	Total (n=16)	p
Age(year)(mean)	10.2	12.9	12± 3.8 years	
Gender, n (%)				
Female	2(40%)	6(54.5%)	8(50%)	0.500
Male	3(60%)	5(45.5%)	8(50%)	
Puberty, n (%)				
Pre-pubertal	2(40%)	3(27.3%)	5(31.2%)	0.516
Pubertal	3(60%)	8(72.7%)	11(68.8%)	
Symptoms, n (%)				
Headache	4(80%)	11(100%)	15(93.8%)	0.313
Vomiting	3(60%)	1(9.1%)	4(25%)	0.063
Nausea	3(60%)	1(9.1%)	4(25%)	0.063
Blurred vision	0(0%)	3(27.3%)	3(18.8%)	0,295
Photophobia	2(40%)	1(9.1%)	3(18.8%)	0.214
Diplopia	0(0%)	2(18.2%)	2(12.5%)	0.458
Hypertension	0(0%)	2(18.2%)	2(12.5%)	0.458
Vertigo	1(20%)	0(0%)	1(6.25%)	0.313
Tremor	1(20%)	0(0%)	1(6.25%)	0.313
Facial numbness	0(0%)	1(9.1%)	1(6.25%)	0.688
Treatment, n (%)				
Acetazolamide	4(80%)	5(45.5%)	9(56%)	0.259
None	1(20%)	6(54.5%)	7(44%)	

have been mentioned as possible but uncommon causes.[6] The explanation for PTC in sinusitis is not clear and it may be secondary to cerebral venous obstruction. Sinusitis can also result in an increase in intracranial pressure that is unrelated to sinus thrombosis.[23] Secondary PTC associated with acute sinusitis was detected in six (37.5%) of our patients. Three patients were diagnosed with maxillary sinusitis, one with frontal sinusitis, and two with both frontal and maxillary sinusitis. PTC associated with maxillary and frontal sinusitis have also been reported in the literature.[6,23]

PTC can rarely occur during the course of SLE. In the active phase of SLE, venous thrombosis occurs in a hypercoagulable state of antiphospholipid antibody syndrome or immune complex, direct antibodies, vasculitis may impair arachnoid villi function, disrupting cerebrospinal fluid (CSF) absorption and producing PTC. [21] Anti-nuclear antibody was positive in our patient, a thrombotic event or vasculitis could be the etiology of PTC in this patient.

Vitamin B12 deficiency and iron deficiency anemia (IDA) have been reported to be associated with PTC.[27,28] Tissue hypoxia due to anemia can result in changes in hemodynamics and permeability in capillaries, resulting in an increase in intracranial pressure. Three of our patients had vitamin B12 deficiency and two of them had IDA.

Vitamin D deficiency has been reported to be associated with PTC in some studies.[23,29] Vitamin D deficiency is accepted as an etiological factor of PTC in the presence of hypocalcaemia and hypophosphatemia in malnutrition and rickets.[23,26] Vitamin D deficiency or low vitamin D did not result in hypophosphatemia or hypocalcaemia in our patients; therefore, it was thought to be an associated finding.

Headache is typical the leading complaint (84% to 92%) of adolescent PTC patients that result in consultation to the physician.[30] Temporary visual disturbances is reported to be seen in 68-72% of PTC patients.[29] It has been reported that persistent development of vision loss was more common in children than adults[29]; whereas none of the patients in our study had permanent vision loss. It was reported that 7-30% of the patients were asymptomatic and were diagnosed incidentally with papillary edema.[30] Blurred vision, diplopia, photophobia were other common symptoms in our patients. Four of our patients were diagnosed with papillary edema during routine eye check without eye symptom. This demonstrates the importance of a careful fundus examination. Papilledema is the characteristic examination finding of PTC and is usually bilateral, similar to our patients.[19,20]

To rule out secondary causes, neuroimaging should involve MRI and MRV. In the various diagnostic criteria all specify that neuroimaging should be normal; all of our patients' MRI and MRV were normal.

The optimal treatment of PTC is still not conclusive. The goal is to lower the intracranial pressure. The carbonic anhydrase enzyme inhibitor acetazolamide is a commonly used in medical treatment. This is thought to act by inhibiting CSF production in the choroid plexus. Topiramate is an antiepileptic drug which has a weak carbonic anhydrase inhibitor. It has been reported that 37.8% and 76.6% of patients responded to acetazolamide treatment.[32] Nine of our patients were treated with acetazolamide and one patient had acetazolamide combined with topiramate. Medical treatment should be continued until papilloedema, headache, vision problems resolve.[6] The follow-up period was between 6-24 months in our study. None of our patients had a vision loss or relapse during the follow up period.

In conclusion, we report here a cohort of Turkish children with PTC. The signs and symptoms of our patients were consistent with what was reported in the literature. Most of our patients were pubertal, and of older age. Patients with secondary PTC had obesity, sinusitis, SLE; low vitamin D, B12 and iron were other associated findings. A quarter of our patients were asymptomatic on diagnosis, demonstrating the importance of fundus examination of children. All our children had full recovery.

DISCLOSURE

Availability of data and material: The datasets used and/or analysed during the current study are available from the corresponding author upon reasonable request.

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Conflicts of interest: None

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