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Original Article

Asymmetric Papilloedema or Normal Cerebrospinal Fluid Pressure Do Not Rule Out Pseudotumour Cerebri

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Abstract ***Objectives:*** Pseudotumour cerebri syndrome (PTC) is an infrequent clinical entity in children, diagnosis and early treatment are essential to prevent potentially irreversible sequelae. This study aims to review our experience with children diagnosed with PTC. ***Methods:*** Demographics data, aetiology, clinical features, fundus examination, neuroimaging studies, treatment, and outcome of patients with PTC were analysed. ***Results:*** Our study group was consisting of nine patients. The most common presenting symptom was headache (77.7%). Unilateral sixth nerve paralysis was the only symptom in one patient. One patient had fulfilled all the modified Dandy criteria except the increased cerebrospinal fluid (CSF) pressure and was evaluated as normal pressure PTC. All patients had bilateral papilloedema, one of them had asymmetric papilloedema. ***Conclusions:*** In this study, we want to emphasize that there may be PTC without increased CSF pressure or with asymmetric papilloedema and unilateral sixth nerve paralysis may be the only finding.

Key words *Asymmetric papilloedema; Normal pressure; Pseudotumour cerebri syndrome; Unilateral sixth nerve paralysis*

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Introduction

Pseudotumour cerebri syndrome (PTC), also known as benign or idiopathic hypertension, is defined as the presence of the signs and symptoms of increased intracranial pressure (ICP) (headache, nausea, vomiting, blurred vision, temporary vision loss), with a normal neurological examination (except for sixth cranial nerve palsy), normal neuroimaging studies and cerebrospinal fluid (CSF) analysis.[1-3] PTC is diagnosed according to modified Dandy criteria shown in Table 1.[4,5]

PTC is not common in children but visual loss due to severe papilloedema is the worst and the most serious complication if no timely treatment is available.[6] No clear consensus on the therapeutic approach exists; the current trend is carefully following the patient or pharmacological treatment, with invasive techniques used only exclusively in patients with severe or recurrent symptoms. Acetazolamide can be used to decrease the CSF production, and multiple lumbar punctures (LP) can be made to decrease ICP.[1,7-10]

This study aims to review the clinical spectrum, investigation findings, and treatment outcome of the paediatric patients with PTC diagnosed over a 2-year period and we want to emphasize that there may be PTC without increased CSF pressure or with asymmetric papilloedema.

Material and Methods

This is a retrospective study of patients diagnosed with PTC at the paediatric neurology department between February 2018 to March 2020. Demographics data, aetiology, clinical features, fundus examination, neuroimaging studies, treatment, and outcome were collected through a systematic review of the electronic medical records. PTC was diagnosed according to modified Dandy criteria shown in Table 1.[4,5] Cranial magnetic resonance imaging (MRI) and magnetic resonance venography (MRV) studies were evaluated in all patients except one (in Case 9 MRV could not be done). A detailed ophthalmological examination was done for all patients (fundus examination and optical coherence tomography to differentiate papilloedema from pseudopapilloedema with buried drusen performed in all patients). LP was performed in all patients. CSF opening pressure, cellular, chemical, and microbiological examination, complete blood count, routine biochemical analysis, acute phase reactant, antinuclear antibodies, serum thyroid-stimulating hormone, serum thyroxine, vitamin D, and vitamin B12 levels were evaluated. All these investigations were done to confirm the diagnostic criteria of PTC and to rule out the other causes of papilloedema. Body mass index (BMI) was calculated and BMI (kg/(m^2) >90th percentile was considered overweight or obese when BMI was >97th percentile. Oral acetazolamide (10-30 mg/kg/day) was started for all patients. The study protocol was approved by the Institutional clinical research ethics committee (2011-KAEK-25 2020/01-22) under the tenets of the declaration of Helsinki.

Results

Our study group was consisting of nine patients (five boys (55.5%) and four girls (44.5%)). The age range was 5.5 to 17 years (median age: 13 years). Eight of the patients (88.8%) fulfilled the modified Dandy criteria, one patient (11.1%) did not meet the increased intracranial pressure criterion. The most common presenting symptom was a headache, which was noted in seven patients (77.7%). The duration of headache before LP was between one to four weeks range. Blurred vision, the first symptom in two patients, was seen in three (33.3%) patients. Visual acuity testing was performed via portable Snellen charts in standard room conditions. Visual acuity assessments were normal in these patients. Duration of the blurred vision was one week in two patients, and six weeks for one patient. Unilateral sixth nerve paralysis was the only symptom in Case 9 who was referred to the paediatric neurology outpatient clinic due to strabismus. Vomiting was an additional symptom of headache in one patient (Case 2). All patients except one had bilateral papilloedema on the ophthalmologic examination, Case 8 had asymmetric papilloedema (Figure 1). Figure 2 shows the optical coherence tomography (OCT) examination of the same patient. Ocular examination showed normal visual acuity in both eyes, no pain with ocular motility, no proptosis. In this case, both MRI and MRV were normal. Demographic properties, clinical characteristics, and tests performed on the patients are shown in Table 2.

All our patients underwent lumbar puncture procedure in a lateral decubitus position with the legs bent. Sedation was performed only in Case 9 who was 5.5 years old. The median CSF opening pressure was 38 cm H_2O (range 11-89 cm H_2O). Case 5 had fulfilled all the modified Dandy criteria except the increased CSF pressure. We

Table 1 Modified Dandy criteria for the diagnosis of pseudotumour cerebri syndrome[4,5]

Signs of intracranial hypertension
Absence of localising signs in the neurological examination, with the exception of the sixth cranial nerve
Absence of pathological neuroimaging findings
Increased cerebrospinal fluid pressure >25 cm H_2O, with normal composition
No other identifiable causes of intracranial hypertension

detected the opening pressure of CSF in LP between normal range (10 cm H_2O) and confirmed this in the second LP after three days (11 cm H_2O) in this patient. Upon vomiting and headache persisted, acetazolamide was started. Headache and papilloedema disappeared after acetazolamide treatment. We evaluated this patient as normal pressure PTC. CSF for cellular, chemical, and microbiological examination, complete blood count, routine biochemical analysis, acute phase reactant, antinuclear antibodies, serum thyroid-stimulating hormone, serum thyroxine, vitamin D, and vitamin B12 levels were detected as normal in all patients. Cranial MRIs were normal in all patients. Cranial MRVs were also normal in 8 patients, in one case cranial MRV couldn't be performed.

Obesity in two patients (22.2%) and hypertension in one patient (11.1%) were determined as an etiological cause. Obese patients were evaluated by the paediatric endocrinologist and the diet was started. The patient with hypertension was evaluated by a paediatric nephrologist, diet, and physical exercise was recommended and no drug was started. After the diagnosis of PTC, oral acetazolamide was applied with an initial dose of 10-20 mg/kg/day in all patients, and the dose was gradually increased (30 mg/kg/day). Patients were seen by ophthalmologists and paediatric neurologist at two-week intervals. LP has not repeated to confirm normalised CSF pressure, symptoms were followed to assess the progression of PTC. The therapy was adjusted according to the patient's symptoms, visual-field examinations, and changes in papilloedema. No other treatment than acetazolamide was needed because the patients' papilloedema had resolved and they had no symptoms. The mean duration of complete resolving of papilloedema was 4.56±2.12 months (range: 2-8 months). The resolution of the symptoms was quick. Headache symptoms disappeared in one week in five patients and three weeks in two patients (mean 1.5 weeks). The visual acuity was normal in all patients at the end of the follow-up period. Acetazolamide treatments were stopped in all patients at the end of the follow-up.

Discussion

The first description of PTC was published by Quincke[11] in 1893. The first diagnostic criteria were established by Dandy[12] in 1937 and subsequently revised by Smith[4] in 1985 to include radiological imaging criteria, and are currently known as the modified Dandy criteria. Scientific progress, further knowledge on this field, and the development of neuroimaging techniques have led to several proposed modifications, such as the one by Rangwala and Liu,[13] adapted to paediatric patients. Laboratory investigations and radiological investigations such as MRI and MRV should be performed to rule out possible causes of raised ICP as in our study.[13] Permanent visual loss may occur as a serious outcome in untreated PTC patients.[14,15]

The spectrum of clinical presentation at the time of diagnosis of PTC was broad-ranging from asymptomatic papilloedema to dramatic clinical presentations such as bilateral abducens palsy. In our series of nine patients, the

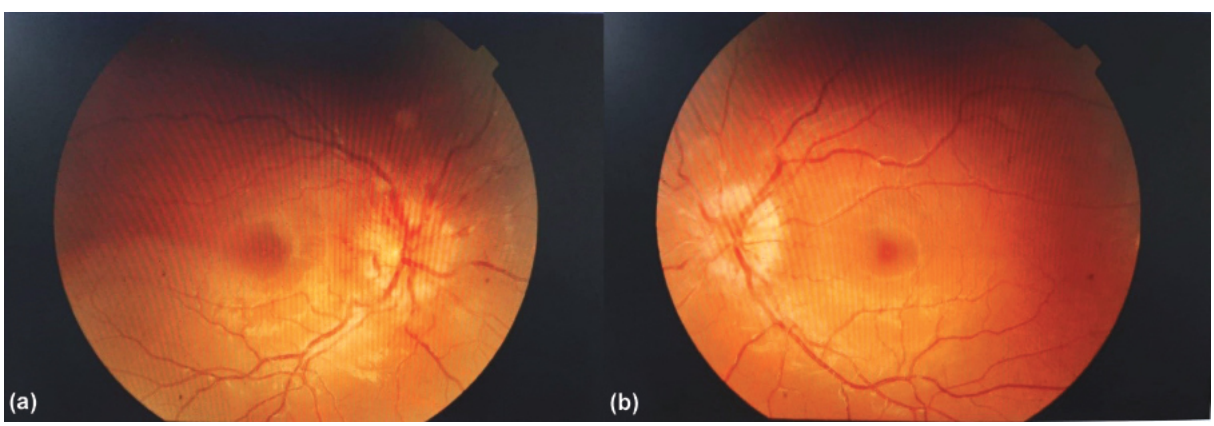

Figure 1 Fundus image of patient 8 with pseudotumour cerebri syndrome. (a) Right swollen optic disc with dilated capillaries and venous tortuosity, retinal nerve fibre layer (RNFL) is seem to be ischaemic in the infero-temporal region of the disc. Splinter-like haemorrhages have existed in all quadrants. (b) Asymmetrically less swollen left optic disc. Relatively normal vascular arcs and there were no splinter-like haemorrhages. RNFL seems to be ischaemic in the infero-temporal region of the disc.

most common presenting symptoms were headache (77.7%) and blurred vision (33.3%). Distelmaier et al[16] reported that the most common clinical presenting symptom was headache and all cases had papilloedema as in our study.

In our study, unilateral sixth nerve paralysis was the only symptom in a patient without headache or other symptoms. Only sixth nerve paralysis is rare without symptoms of increased intracranial pressure in PTC. In a study of 78 children with PTC, two patients had unilateral and four patients had bilateral sixth nerve paralysis. In comparison, it's stated that the sixth nerve paralysis patients had a higher BMI and opening pressure.[17]

Distelmaier et al also reported four out of twelve children presented with no obvious symptoms and papilloedema was found on routine eye examination.[16] These data have again shown how important the evaluation of fundus examination in a child with suspected raised ICP. The ophthalmological study, including eye fundus examination and visual field assessment, is essential for diagnosis, follow-up, and deciding treatment aggressiveness. The first diagnostic approach should differentiate between papilloedema and pseudopapilloedema and rule out other causes of papilloedema, such as optic neuritis, ischaemic optic neuropathy, or neuroretinitis.[18,19] Diagnosis occasionally requires an ocular ultrasound, optical coherence tomography, or a fluorescein angiography to confirm the presence of papilloedema and rule out causes of pseudopapilloedema such as optic nerve drusen.[20,21] In our study, all patients had papilloedema and one of them had asymmetric papilloedema. While bilateral papilloedema is frequently detected in PTC, unilateral papilloedema is rare. The exact cause is not known, various hypotheses have been proposed such as anomalous optic nerve sheath, variations of the trabecular meshwork of fibrous adhesions in the subarachnoid space surrounding the optic nerve, and the anatomical difference in lamina cribrosa.[22-25]

LP should be performed in papilloedema, which is not accompanied by pathological neuroimaging findings.

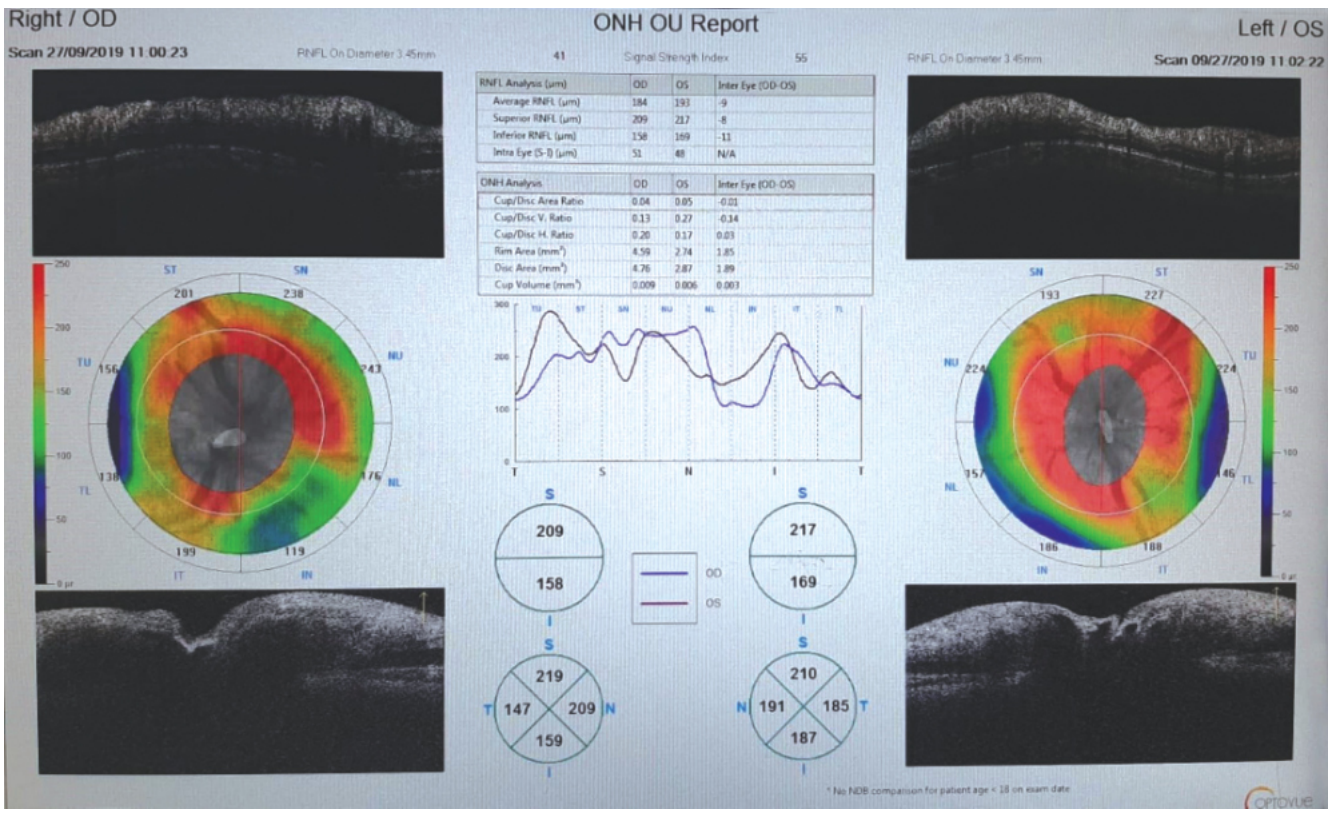

Figure 2 Optical coherence tomography examination of patient 8. The retinal nerve fibre layer (RNFL) thicknesses were similar between right and left eyes. Please note the similar and normal route of the retinal pigment epithelium and Bruch's membrane at the level of the scleral channels.

Measuring CSF pressure in children is not simple; changes in opening pressure are reported to be influenced by several factors, including age (values in children older than 8 are reported to be similar to those of adults), Valsalva maneuvres, or the patient's position.[7,8] A recent prospective study conducted to establish opening pressure in paediatric patients found increased pressure to be significantly associated with sedation and higher BMI. These authors propose that an opening pressure ≥28 cm H_2O should be considered abnormally elevated (25 cm H_2O if the patient is not obese or sedated).[9] In our study, sedation was performed only in Case 9 who was 5.5 years old and CSF opening pressures of the patients were in the 10 to 89 cm H_2O range (median 38 cm H_2O). Case 5 had fulfilled all the modified Dandy criteria except the increased CSF pressure. We detected the opening pressure of CSF between the normal range (10 cm H_2O) and confirmed this in the second LP (11 cm H_2O). Upon vomiting and headache persisted, acetazolamide was started in this patient. Headache and papilloedema disappeared after acetazolamide treatment. We evaluated this patient as normal pressure PTC. A variant of PTC known as "Normal Pressure Pseudotumour Cerebri" has the same features of PTC except for normal opening pressure. Recurrent LP or 24 hours ICP monitoring is suggested in patients who are suspected of having PTC but have a normal CSF pressure.[26] Abdelfatah[27] reported six patients with normal pressure PTC and suggested to reserve continuous ICP monitoring for those cases that had a normal opening pressure in the first LP and a higher opening pressure in the second LP. If the patient has typical clinical features of PTC, such as papilloedema and blind spot enlargement, it was emphasized that the diagnosis of PTC should be kept in mind even if the CSF pressure is normal. Also, Suh and Kim reported two cases of normal pressure pseudotumour cerebri patients one of which is 15 years old girl.[28] The exact cause of normal pressure PTC is not yet known. The unilateral papilloedema mechanism and normal CSF pressure may be related to similar mechanisms.

The association of PTC with obesity and overweight higher are in adolescents than in young children.[29] In our study, two patients (22.2%) were obese and one of them had hypertension (11.1%). Our findings are similar to another study in which obesity was found in three of twelve patients.[16]

There is no consensus algorithm for the treatment of this condition since there are no randomised studies to support evidence-based treatment. The first-line drug for children is acetazolamide. The other medical treatment alternatives are furosemide, corticosteroids, or topiramate to complement or substitute treatment.[1-3] In a study, 60 children who were diagnosed with PTC were treated with acetazolamide as first-line therapy with a response rate characterised by resolution of symptoms and papilloedema as high as 76.6%.[30] Schoeman gave acetazolamide and furosemide combination treatment to 8 children and all patients respond quickly and symptoms were relieved.[31]

We applied acetazolamide treatment to all patients and continued till the complete disappearance of papilloedema. The visual acuity was normal in all patients at the end of the follow-up period. Our patients whose symptoms

Table 2 Clinical characteristics of patients

Patient	Age/Sex	Symptoms	Aetiology	Papilloedema	CSF-OP (cm H_2O)	Cranial MR/ MR venography	Treatment	Papilloedema resolution (Months)
1	12/F	Headache	Obesity	Bilateral	51	N/N	ACT	4
2	14/F	Headache, Vomiting	Unknown	Bilateral	55	N/N	ACT	4
3	11/F	Blurred vision	Unknown	Bilateral	80	N/N	ACT	6
4	13/M	Headache	Obesity, hypertension	Bilateral	30	N/N	ACT	5
5	16/F	Headache	Unknown	Bilateral	11	N/N	ACT	7
6	13/M	Headache	Unknown	Bilateral	27	N/N	ACT	8
7	17/M	Headache Blurred vision	Unknown	Bilateral	34	N/N	ACT	2
8	16/M	Headache Blurred vision	Unknown	Unilateral	89	N/N	ACT	2
9	5.5/M	Unilateral paralysis of the 6th cranial nerve	Unknown	Bilateral	38	N/	ACT	3

CSF-OP: cerebrospinal fluid opening pressure (cm H_2O), ACT: acetazolamide

gradually improved after acetazolamide administration did not require medical treatment changes or unloading LP.

In conclusion, while PTC is an infrequent clinical entity in children, diagnosis and early treatment are essential to prevent potentially irreversible sequelae. PTC may present as unilateral or asymmetric papilloedema or unilateral sixth nerve paralysis in an asymptomatic patient or normal pressure CSF, except for the classical modified Dandy criteria. Based on the common feature of our patients, PTC should be kept in mind in patients with papilloedema and normal neuroimaging findings.

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Declaration of Interest

None

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