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Pseudotumor cerebri in childhood and adolescence: data from a specialized service

Pseudotumor cerebral na infância e adolescência: dados de um serviço especializado

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ABSTRACT

Objective: To report cases of children and adolescents diagnosed with pseudotumor cerebri associated or not with rheumatic disease. **Methods:** This was a retrospective study based on medical reports of 29 patients, up to 18 years of age and diagnosed with pseudotumor cerebri, followed up in the Pediatric Rheumatology and Neurology outpatient clinics of a tertiary hospital, until December 2016. **Results:** Among the 29 patients diagnosed with pseudotumor cerebri, 51.7% were girls and the mean age at the disease onset was 12.3 years. In 18 patients (62%) where an etiology was found, four were associated with a rheumatic disease. The most common symptom was headache (69%) and acetazolamide was the most used medication (69%). Two patients developed blindness and 10 are still being followed up. **Conclusion:** Although rare, pseudotumor cerebri should be considered in children with headaches, especially in patients with rheumatic disease.

Keywords: Pseudotumor cerebri; headache; rheumatic diseases; childhood.

RESUMO

Relatar os casos de crianças e adolescentes com diagnóstico de pseudotumor cerebral com ou sem doença reumática. **Métodos:** Estudo retrospectivo através de revisão de prontuários, 29 pacientes com idade até 18 anos e diagnóstico de pseudotumor, atendidos nos ambulatórios de Reumatologia Pediátrica e Neurologia de um hospital terciário, registrados até dezembro de 2016. **Resultados:** Dentre os 29 pacientes com diagnóstico de pseudotumor cerebral, 51,7% eram meninas. A média de idade de aparecimento dos sintomas foi de 12,3 anos. Em relação à etiologia do pseudotumor cerebral, em 18 pacientes (62%) foi possível identificar uma causa, sendo o diagnóstico de doença reumática associada em quatro desses casos. Cefaléia foi o sintoma mais frequente (69%), e a medicação mais utilizada foi a acetazolamida (69%). Dois pacientes evoluíram para cegueira e 10 ainda se encontram em seguimento ambulatorial. **Conclusão:** Concluímos que, apesar de raro, o diagnóstico de pseudotumor cerebral deve ser considerado em crianças com cefaleia, principalmente nos pacientes com doença reumática.

Palavras-chave: Pseudotumor cerebral; cefaleia; doenças reumáticas; infância.

Pseudotumor cerebri, or benign intracranial hypertension, is a syndrome that presents with clinical features of elevated intracranial pressure without radiological evidence of an intracranial mass, infection, vascular abnormality, hydrocephalus or changes in the level of consciousness[1,2,3,4,5].

The incidence of pseudotumor cerebri in general population is 1:100,000. It is rare in childhood. The incidence increases between the ages of 12 and 15 years, and 60% of the children who develop the syndrome are over 10 years of age[2,6,7,8].

The pathogenesis of pseudotumor cerebri is still unknown; some hypotheses include decreased absorption of cerebrospinal fluid (CSF) associated with vascular resistance in the sinus[2,7,9,10,11].

Several conditions are associated with pseudotumor cerebri (secondary pseudotumor), such as systemic diseases and drug exposure. The term idiopathic intracranial hypertension is used when the cause of this condition is not found[12,13,14].

There are few studies in the literature, most of which are case reports, describing secondary pseudotumor syndrome in Pediatrics. Our objective was to report all cases of children and adolescents diagnosed with pseudotumor cerebri, with or without rheumatic disease, who were followed by the pediatric rheumatologists and neurologists of our hospital.

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METHODS

This was a retrospective cohort study evaluating 29 patients, up to 18 years of age, with the diagnosis of pseudotumor cerebri according to the criteria of Dandy et al.[15,16] modified by Rangwala and Liu[17]. Patients were selected from the Pediatric Rheumatology and Neurology outpatient clinics of the Federal University of São Paulo, in Brazil, until December 2016. The following data were analyzed: demographics, pseudotumor etiology, clinical features, treatment and outcome. All patients underwent diagnostic spinal manometry with opening pressure equivalent to or greater than 25 mm of water[17].

RESULTS

Of the 29 patients, 51.7% (15 patients) were girls. The mean age of symptom onset was 12.3 ± 4.3 years. The mean age at first evaluation was 15.4 ± 4.4 years.

Regarding the etiology of the pseudotumor cerebri, 11 (37.9%) patients were diagnosed with idiopathic pseudotumor and 18 patients (62.1%) had secondary pseudotumors. In four of these latter patients (13.8%) a rheumatic disease was identified. Among these, two had juvenile dermatomyositis undergoing oral glucocorticoid withdrawal. One patient had Henoch-Schönlein purpura, and was also receiving glucocorticoids. The fourth patient presented with antiphospholipid antibody syndrome. Other causes were obesity/overweight (three patients), use of drugs such as tacrolimus and growth hormone (two), renal transplantation (two), cavernous sinus thrombosis (two), hypervitaminosis A (one), Bardet-Biedl syndrome (one), cranial trauma (one), immune thrombocytopenic purpura (one), and cavernous angioma (one). Table 1 shows the demographic characteristics and etiology of the pseudotumor cerebri patients.

The most frequent symptoms and signs were: papilledema and headaches in 20 patients (69.0%), decreased visual acuity in 16 (55.2%), and nausea and vomiting in seven (24.1%).

Headache occurred in 13 patients with secondary pseudotumor and in seven patients with primary pseudotumor. The most frequent characteristics of the headaches were: holocranial location with nuchal irradiation, continuous, worse at night and in the mornings and in some cases associated with nausea and vomiting.

Table 2 shows the signs and symptoms presented by each patient.

Imaging studies were performed on all patients. The findings included: empty sella, prominent gyri and sulci, and optic nerve sheath edema.

The most commonly-used medication was acetazolamide as monotherapy in 20 (69.0%) patients and in combination with topiramate in four (13.8%) patients. Nine (31.0%) patients did not use any drug treatment. Table 3 shows the treatment for each patient.

Table 1. Demographic characteristics and etiology of cerebral pseudotumor in 29 patients.

Patient	Sex	Age diagnosis (years)	Etiology
1	Male	14	Renal transplantation
2	Male	9	Idiopathic
3	Male	18	Hypervitaminosis A
4	Female	14	Cavernous sinus thrombosis
5	Male	6	Idiopathic
6	Male	17	Renal transplantation
7	Female	12	Cavernous angioma
8	Male	6	Cranial trauma
9	Female	18	Idiopathic
10	Male	10	Idiopathic
11	Male	10	Idiopathic
12	Female	12	Obesity
13	Female	16	Overweight
14	Female	10	Growth hormone use
15	Female	17	Idiopathic
16	Male	11	Idiopathic
17	Female	19	Bardet-Biedl syndrome
18	Female	8	Idiopathic
19	Female	18	Idiopathic
20	Female	9	Antiphospholipid syndrome
21	Female	5	Juvenile dermatomyositis
22	Female	18	Idiopathic
23	Male	15	Idiopathic
24	Female	13	Tacrolimus use
25	Female	14	Obesity
26	Male	6	Henoch-Schönlein Purpura
27	Male	7	Immune thrombocytopenic purpura
28	Male	15	Cavernous sinus thrombosis
29	Male	12	Juvenile dermatomyositis

Regarding the outcome, there was a resolution of the condition in 27 patients. Two patients developed blindness (partial/total) due to pseudotumor cerebri and there were no deaths. The median of time until clinical resolution was 120 days (ranging from 14 to 1,800 days) and 10 patients are still being followed up as outpatients.

DISCUSSION

Pseudotumor cerebri is a rare condition in childhood and adolescence. Association with other entities and prognosis differ from the adult presentation due to lower rates of chronicity and recurrence[8,18]. In our study, we observed a

Table 2. Signs and symptoms presented by 29 patients with cerebral pseudotumor.

Patient	Headache	Nausea/vomiting	Visual loss	Papilledema
1	No	No	No	No
2	Yes	No	Yes	Yes
3	Yes	No	Yes	Yes
4	No	No	No	No
5	No	No	No	No
6	Yes	No	Yes	Yes
7	Yes	Yes	Yes	Yes
8	Yes	No	Yes	No
9	Yes	v	Yes	Yes
10	Yes	Yes	Yes	Yes
11	No	Yes	No	Yes
12	Yes	Yes	No	Yes
13	Yes	No	Yes	Yes
14	Yes	No	No	Yes
15	Yes	No	Yes	No
16	No	No	No	Yes
17	Yes	No	Yes	No
18	No	No	No	Yes
19	Yes	Yes	No	Yes
20	Yes	No	Yes	Yes
21	Yes	No	No	Yes
22	Yes	No	No	No
23	No	No	Yes	Yes
24	Yes	No	Yes	Yes
25	Yes	No	Yes	Yes
26	No	No	No	No
27	No	No	Yes	Yes
28	Yes	Yes	No	No
29	Yes	Yes	Yes	Yes

Table 3. Treatment of 29 patients with cerebral pseudotumor.

Patient	Medication	Lumbar puncture	Spinal shunt
1	No	No	No
2	Acetazolamide	No	No
3	Acetazolamide	Yes	No
4	No	No	No
5	No	No	No
6	Acetazolamide	Yes	No
7	Acetazolamide	Yes	No
8	Acetazolamide	Yes	Yes
9	No	No	No
10	Acetazolamide + Slow-K	No	No
11	Acetazolamide	No	No
12	Acetazolamide + Topiramate	No	Yes
13	No	Yes	Yes
14	Acetazolamide + Topiramate	Yes	Yes
15	Acetazolamide	No	No
16	Acetazolamide	No	No
17	No	Yes	Yes
18	Acetazolamide + Slow-K	No	No
19	Acetazolamide + Topiramate	No	Yes
20	Acetazolamide + Bicarbonate	No	Yes
21	Acetazolamide	No	Yes
22	Acetazolamide	No	No
23	Acetazolamide	No	No
24	Acetazolamide	No	No
25	Acetazolamide + Topiramate	No	No
26	No	No	No
27	No	Yes	No
28	No	Yes	No
29	Acetazolamide	No	No

predominance of secondary disease with an association with rheumatic diseases in about a quarter of the identifiable etiologies. We found a positive outcome in most cases, with the exception of visual sequelae in two patients.

The mean age of onset of the pseudotumor cerebri was approximately 12 years and the youngest patient was five years old. This finding is consistent with Babikian et al., who reported that approximately 60% of pediatric patients with pseudotumor cerebri were 10 years of age or older[19]. Disease frequency increases with age and peaks in adolescence[3]. In our study, sex did not influence the frequency of the disease[8,20].

Clinical criteria are well established. We used Dandy's[15] criteria, modified by Friedman and adapted for children by Rangwala and Liu[16]. The definition of normal spinal manometry is still controversial. Several authors postulate that opening pressure is related to the age group and to the presence or absence of papilledema[2,17,21]. Headache relief after lumbar puncture is an alert for the diagnosis of pseudotumor[22].

The most frequent signs and symptoms in our study were papilledema and headaches, followed by visual loss. Most authors describe headache as the most common symptom (61% to 94% of cases)[18]. In the study by Tibussek et al., headache was described as chronic, daily, or mimicking acute migrane[23].

In our study, four patients were diagnosed with pseudotumor secondary to rheumatic diseases; glucocorticoid was used in three of these patients (two in tapering doses); and there was one case related to antiphospholipid syndrome. The study by Sussman et al.[24] showed that prothrombotic events play an important role in the pathogenesis of pseudotumor. The presence of antiphospholipid antibodies was observed

in 32% of the patients[24]. Leker and Steiner's study[25] described the association of pseudotumor cerebri and the presence of anticardiolipin in six of 14 patients (43%), suggesting anticardiolipin as a risk factor for a thrombotic cause of pseudotumor cerebri. The presence of these antibodies was assessed only in the patient with antiphospholipid syndrome.

The role of glucocorticoid tapering in triggering pseudotumor has been described. Although the pathogenesis is unknown, patients with onset of headaches after glucocorticoid discontinuation should be evaluated for intracranial hypertension with eye fundoscopy, CSF examination and imaging[25]. However, glucocorticoids are not recommended for the treatment of children with chronic pseudotumor cerebri because of their adverse effects, such as weight gain and rebound of intracranial hypertension during periods of medication tapering[25,26].

Conditions of hypercoagulability, such as in Behçet's disease and systemic lupus erythematosus, may lead to dural sinus thrombosis and pseudotumor[22]. There are no descriptions in the literature of pseudotumor associated with juvenile dermatomyositis or Henoch-Schönlein purpura in childhood. Therefore, we believe that the true cause of pseudotumor in our patients may have been glucocorticoid tapering, since all patients were receiving this medication in progressively smaller doses. Case reports of patients with Cushing's syndrome have shown that treating hypercortisolism with drugs such as ketoconazole could trigger pseudotumor cerebri[27].

One of the most frequent causes of pseudotumor in adult patients is obesity[9,10]. However, only three patients in our group were obese.

Similar to the literature, the first-choice medication was acetazolamide (20 patients), followed by topiramate. Both drugs reduce the production of CSF. Acetazolamide decreases the severity of headaches, reduces the risk of papilledema and stabilizes visual function[19]. Current knowledge shows no benefit in multiple relief lumbar punctures due to uncertain results, technical difficulties, need for sedation and rapid reestablishment of previous CSF levels. Some authors recommend the use of glucocorticoids to control CSF production, but their use is restricted to cases of severe headache, severe papilledema and very high intracranial pressure[18,25,26]. A spinal shunt was performed in seven patients due to failure of clinical treatment. Nine patients did not receive medication because their headaches improved after lumbar puncture.

Papilledema in childhood usually disappears after three to six months of treatment, although in some cases it may last longer and lead to atrophy of the optic nerve[18]. Visual loss at onset was reported in 6% to 20% of pediatric cases, although loss of the visual field may occur in up to 91% of these patients[18]. We observed visual loss in two patients. Studies show that children have an increased risk of permanent visual loss due to papilledema[12].

Among the positive points of our study, we emphasize the description of pseudotumor cerebri associated with rare systemic conditions in pediatric patients, such as in rheumatic diseases. This is a rare and entity that can lead to permanent damage. This study was a pioneer in reporting cases of pseudotumor cerebri associated with juvenile dermatomyositis and Henoch-Schönlein purpura, although the most-likely cause in these patients was glucocorticoid withdrawal.

Since this was a retrospective study, it was impossible to detail the data, such as doses and glucocorticoid reduction. In addition, there was a small number of patients and, in some of them, the determination of antiphospholipid antibodies was not performed.

Although rare, pseudotumor cerebri is a clinically severe syndrome that can cause permanent visual loss in children if not promptly diagnosed. Rheumatic disorders are important causes of this syndrome.

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