Idiopathic intracranial hypertension in children and adolescents in southern Brazil

Hipertensão intracraniana idiopática em crianças e adolescentes no sul do Brasil

Hipertensión intracanal idiopática en niños y adolescentes del sur de Brasil

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Abstract

Introduction: Idiopathic intracranial hypertension (IIH) is a syndrome characterized by signs and symptoms of elevated intracranial pressure without the identification of tumor or ventriculomegaly. The aim of this study is to evaluate the epidemiological profile of children diagnosed with IIH in southern Brazil. Methods: This is a retrospective study, through the analysis of medical records and complementary exams. The medical records of patients diagnosed with IIH from January 2012 to September 2022 were evaluated. Results: Data from 33 children were analyzed and the mean age at diagnosis was 9 years, 66.7% of whom were female. In patients less than 8 years of age, the mean weight Z-score was -0.32 (SD :1.88). Of the analyzed patients, 66.7% had symptoms for up to one month, 93.3% had primary IIH and 86.7% had headache as the first symptom. Regarding treatment, 90.0% responded to monotherapy and 13.3% required surgical intervention. There was a higher risk of surgery in patients who had higher cerebrospinal fluid opening pressure at diagnosis (p=0.029). Visual sequelae at hospital discharge were observed in 47.1% of patients. Conclusion: Clinical signs and symptoms can be variable in pediatrics, requiring additional tests. A higher prevalence of IIH was observed in female adolescents. There is an increase in incidence over time, which reinforces the care and attention for this condition in pediatrics.

Keywords: Pseudotumor; Idiopathic intracranial hypertension; Papilledema; Pediatrics.

Resumo

Introdução: A hipertensão intracraniana idiopática (HII) é uma síndrome caracterizada por sinais e sintomas de elevação da pressão intracraniana sem identificação de tumor ou ventriculomegalia. O objetivo deste estudo é avaliar o perfil epidemiológico de crianças com diagnóstico de HII no sul do Brasil. Métodos: Trata-se de um estudo retrospectivo, por meio da análise de prontuários e exames complementares. Foram avaliados os prontuários de pacientes diagnosticados com HII no período de janeiro de 2012 a setembro de 2022. Resultados: Foram analisados dados de 33 crianças e a média de idade ao diagnóstico foi de 9 anos, sendo 66,7% do sexo feminino. Em pacientes com menos de 8 anos de idade, o escore Z de peso médio foi -0,32 (DP:1,88). Dos pacientes analisados, 66,7% apresentavam sintomas por até um mês, 93,3% apresentavam HII primária e 86,7% apresentavam cefaleia como primeiro sintoma. Em relação ao tratamento, 90,0% responderam à monoterapia e 13,3% necessitaram de intervenção cirúrgica. Houve maior risco de cirurgia em pacientes que apresentavam maior pressão de abertura do líquido cefalorraquidiano ao diagnóstico (p=0,029). Sequelas visuais na alta hospitalar foram observadas em 47,1% dos pacientes. Conclusão: Os sinais e sintomas clínicos podem ser variáveis em pediatria, necessitando de exames complementares. Maior prevalência de HII foi observada em adolescentes do sexo feminino. Há aumento da incidência ao longo do tempo, o que reforça o cuidado e a atenção com essa condição na pediatria.

Palavras-chave: Pseudotumor; Hipertensão intracraniana idiopática; Papiledema; Pediatria.

Resumen

Introducción: La hipertensión intracraneal idiopática (HII) es un síndrome caracterizado por signos y síntomas de presión intracraneal elevada sin identificación de tumor o ventriculomegalia. El objetivo de este estudio es evaluar el perfil epidemiológico de los niños diagnosticados con HII en el sur de Brasil. Métodos: Este es un estudio retrospectivo, a través del análisis de historias clínicas y exámenes complementarios. Se evaluaron las historias clínicas de los pacientes diagnosticados con HII desde enero de 2012 hasta septiembre de 2022. Resultados: Se analizaron los datos de 33 niños y la edad media al diagnóstico fue de 9 años, de los cuales el 66,7% eran mujeres. En pacientes menores de 8 años, el Z-score de peso medio fue de -0,32 (DE: 1,88). De los pacientes analizados, el 66,7% presentaba síntomas hasta un mes, el 93,3% presentaba HII primaria y el 86,7% presentaba cefalea como primer síntoma. En cuanto al tratamiento, el 90,0% respondió a la monoterapia y el 13,3% requirió intervención quirúrgica. Hubo un mayor riesgo de cirugía en los pacientes que tenían una mayor presión de apertura del líquido cefalorraquídeo en el momento del diagnóstico (p = 0,029). Se observaron secuelas visuales al alta hospitalaria en el 47,1% de los pacientes. Conclusión: Los signos y síntomas clínicos pueden ser variables en pediatría, requiriendo exámenes adicionales. Se observó una mayor prevalencia de HII en mujeres adolescentes. Hay un aumento de la incidencia a lo largo del tiempo, lo que refuerza el cuidado y la atención de esta patología en pediatría. **Palabras clave:** Pseudotumor; Hipertensión intracraneal idiopática; Papiledema; Pediatría.

1. Introduction

The *pseudotumor cerebri syndrome* (PTCS) is a condition that presents a series of symptoms and signs that reflects in the increase of intracranial pressure with normal brain parenchyma, and this cannot be attributed to a lesion such as, ventriculomegaly, malignancy or infection (Cleves-Bayon, 2018). In pediatric studies the incidence of PTCS is estimated at 0.6 - 0.71/100,000 (Balbi et al, 2018; Mollan, 2018; Tovia et al, 2017).

When there is an identifiable secondary cause such as drugs (hypervitaminosis A, tetracycline, retinoic acid), endocrine-metabolic diseases (thyroid diseases, hyperparathyroidism), autoimmune syndromes and diseases, and venous abnormalities [1–3, 6], it is characterized as secondary intracranial hypertension (Cleves-Bayon, 2018; Balbi et al, 2018; Mollan, 2018; Tovia et al, 2017). In cases where PTCS does not have a known etiology, it is called idiopathic intracranial hypertension (IIH). This syndrome can cause permanent vision loss in up to 33% and headache in up to 98% of pediatric patients with this condition (Kohli et al, 2019).

In children and adolescents, it is a rare condition and it was necessary to modify Friedman's Dandy criteria (Cleves-Bayon, 2018; Mollan et al 2018; Kohli et al, 2019; Friedman et al 2013), due to the higher opening pressure in lumbar puncture (LP) in children (Cleves-Bayon, 2018; Lalou AD et al, 2020), in addition to include criteria that confirm the diagnosis even in the absence of papilledema, a cardinal sign of the syndrome (Friedman DI et al, 2013; Barmherzig, Szperka, 2019).

There is a well-defined relationship between the disease and the female gender and obesity, both in the adult and pediatric populations at pubertal age, but the literature still lacks studies on prepubertal age (Mollan, et al 2018; Boles et al 2019).

The annual incidence of PTCS in adults is estimated at 0.9 - 2.36/100,000 (Mollan SP et al 2018; Tovia E et al, 2017), while in pediatrics the annual patients, there is still not enough research to draw a robust epidemiological profile and the outcome of these cases. There is also a percentage of cases refractory to clinical treatment, requiring neurosurgical intervention to improve the clinical picture and often decompression of the optic nerve, which includes the approach of specialized ophthalmologists for clinical and surgical management (Cleves-Bayon, 2018; Mollan et al 2018; Bhala et al, 2019).

Thus, the objective of this study is to evaluate the epidemiological profile of children diagnosed with IIH in a University Hospital in southern Brazil, identifying etiology and prognostic factors.

2. Methodology

A cross-sectional observational retrospective study was carried out (Pereira et al, 2018), through the analysis of medical records and complementary exams of pediatric patients aged 0 to 18 years, diagnosed with IIH in the period from

January 2001 to September 2022, available in the electronic system of a hospital discharge service. of high complexity and reference in pediatrics in Brazil. The present study was approved by the Research Ethics Committee of Hospital Pequeno Príncipe under protocol CAAE: 35811120.8.0000.0097.

For the diagnosis of IIH, Friedman's criteria were used (Friemanm et al, 2013). Participants initially eligible for the study were individuals of both sexes, with no restrictions on ethnicity or social group, aged between 2 years and 17 years, 11 months and 29 days.

To include patients in the study, their medical records had to include information on age at diagnosis, clinical status, estimated onset of symptoms, associated comorbidities, weight, instituted treatment, data on treatment initiation, visual acuity at discharge, and presence of papilledema at discharge. After lumbar puncture, manometry was performed on all included patients according to the protocol already established at the hospital.

The primary and secondary classification of IIH described by Sheldon et al. (2017), was used. Secondary IIH was diagnosed when IIH was attributable to one or more identifiable causes, including medications, hormones, and medical conditions other than obesity alone.

The variables that did not contain information in the medical record and, therefore, were not evaluated in any patient were the presence of magnetic resonance imaging of the orbit and magnetic resonance venography. In addition, no patient underwent fenestration of the optic nerve sheath and, therefore, it was not possible to collect this information. It was not possible to assess obesity using the Body Mass Index (BMI) in all patients, due to the lack of height data in the submitted medical records. Weight values were classified according to the Z-score according to the standardization of the World Health Organization (WHO).

Data was organized and stored in a Microsoft Excel spreadsheet. The analysis was performed using the SPSS program, version 25.0. Descriptive results will be presented using means, minimum and maximum values (quantitative variables), and frequencies and percentages (qualitative variables). Analytical results were performed using the chi-square test and Student's t test, P values less than 0.05 were considered significant.

3. Results

Thirty participants met the inclusion criteria, but four were excluded due to medical records and two were withdrawn because, although initially attempted for IIH, it progressed over time to hydrocephalus. Mean age at diagnosis was 9 years (SD: 4.2), median 9 (1 – 17 years), 66.7% (20) were female, Figure 1.



Figure 1 - Frequency of age and gender of patients with Idiopathic Intracranial Hypertension.



Among the thirty patients, 9 patients had complete information on weight and height, in order to assess BMI. Of these 9 patients, 66.6% had a BMI greater than 25. The mean weight Z score was +0.99 (SD:1.50), ranging from -3.64 + 3.90. Eight patients, 27% were overweight, 4 of them aged over 10 years.

When categorized by age, in patients less than 8 years of age, the mean weight z-score was 0.67 (SD:1.49), while patients 8 years and older had a mean weight z-score of + 1.22 (SD:1.52), with no difference between these groups (p=0.033). There was no difference between the mean Z-score for weight between patients with primary or secondary etiology (p=0.260), with mean respectively of 1.16 (SD:1.30) and 0.10 (SD:1.75).

Of the analyzed patients, 66.7% had symptoms for up to one month, demonstrating an early diagnosis. 73.3% are in the capital and metropolitan region (possibility of difficult referral to other cities and/or lack of diagnosis). The number of IIH diagnoses per year is summarized in Figure 2.



Figure 2 - Number of patients with Idiopathic Intracranial Hypertension identified.



When assessing the etiology of the pseudotumor, 28 patients (93.3%) were affected as the primary cause. Among them, there were two cases of secondary intracranial hypertension, one with Down syndrome and the other with systemic lupus

erythematosus. There was no difference between age according to primary or secondary etiology (p=0.94), with a mean of 7.71 (SD 4.11) and 8.50 (SD 7.78), respectively.

As for signs and symptoms, 26 patients (86.7%) had headache; 10 (33.3%) visual blurring; 13 (43.3%) vomiting; 11 (36.78%) nausea; 6 (27.3%) photophobia; 7 (23.3%) diplopia; 6 (20.0%) strabismus and 1 (3.3%) were asymptomatic. 20 (66.6%) patients had headache as the first symptom.

Analyzing the MRI of the brain, 8 (30.0%) patients had optic nerve tortuosity, 6 (20.0%) eyeball rectification and 3 (10.0%) patients had empty sella. Another 5 (13.3%) patients had different alterations not related to the syndrome (IIH).

Among the therapeutic alternatives, 27 (90.0%) received acetazolamide and this was chosen as the first line in 80.0% of the cases; 11 (36.7%) were using topiramate and 4 (13.3%) had a lumboperitoneal shunt. Methylprednisolone was used in 11 patients (36.7%). When assessing treatment response, 60% (n=18/30) of patients responded to acetazolamide monotherapy. There was no difference in response to acetazolamide between primary/secondary forms (p=0.591), age (p=0.429), weight (p=0.567) or time from onset of symptoms to treatment (p=0.995).

The opening pressure of patients who responded to acetazolamide monotherapy (M:39.11; SD:13.54) was lower than those who required polytherapy or surgical intervention (M:69.01; SD:77.88) (p=0.029).

Surgical intervention was required in 4 (13.3%) patients. There was a greater risk of surgery in patients who had higher cerebrospinal fluid (CSF) opening pressure at diagnosis (p=0.71), with a mean of 37.8 mmHg (SD :13.49) in those who did not require surgery versus average of 40.4 mmHg (SD:15.9) in those requiring surgery. There was no greater risk of therapeutic indication when assessing age (p=0.92) or disease duration (p=0.67). Visual sequelae at hospital discharge were observed in 26.7% of patients (n=8/30).

4. Discussion

Pseudotumor cerebri is a rare condition in childhood and adolescence, that is, there is a description in the literature both in the prepubertal and pubertal phases. In our study, we found a higher prevalence of primary pseudotumor, that is, idiopathic intracranial hypertension in 28 patients (93.3%). There was a predominance of females in different age groups, which corroborates the literature (Balbi et al, 2018; Phillips, 2012).

The mean age for diagnosis and onset of IIH was lower than that found in other studies, IIH (n=28) was 9 years old and the youngest patient was one year old (Cleves, 2018; Balbi, 2018; Philips, 2012; Medina et al, 2014). As it is a pediatric reference center, there may have been an early referral, in addition to greater ease and agility in performing specific exams. This is rich data, as the literature presents many reports of pubescent or older patients. The frequency of the disease increases with age and has its peak in adolescence, which corroborates the literature (Balbi et al, 2018; Phillips, 2012).

Another interesting point to be observed is the increase in the diagnoses over the years. This increase may be related to the diagnostic criteria for pseudotumor, which were changed in 2013, taking into account the imaging findings, the patient's clinical condition and the CSF opening pressure. In a study carried out in Wales, a considerable increase in the incidence and prevalence of IIH was observed, with 7.8/100,000 person-years in 2003 and 76/100,000 in 2017 (Strafford et al, 2020; Miah et al, 2021). The COVID19 pandemic, which started in 2019, may have caused a delay and a decrease in diagnoses, due to the reduction in referrals and contingency plans aimed at combating the coronavirus.

Primary IIH was predominant in the study, as pointed out by most studies (Cleves-Bayon et al, 2018; Sheldon et al, 2017; Bhalla et al, 2019). In contrast, Balbi et al (2018), report the secondary form as predominant. Classically, secondary forms refer to a clinical diagnosis attributable to one or more of a variety of identifiable causes, medications, and other medical conditions beyond obesity alone (Sheldon et al, 2017). In our study, there were the two most commonly described secondary causes, one with Down syndrome and the other with systemic lupus erythematosus (Balbi et al, 2018). All these citations

reinforce the secondary diagnoses found in the patients. There are still not enough studies in children to determine whether the prevalence is higher in primary or secondary cases (Wall et al, 2014). [20].

The most prevalent symptoms are in accordance with the literature, with headache being the most prevalent symptom of IIH, followed by blurred vision, nausea and vomiting (Cleves-Bayon, 2018; Balbi et al, 2018; Philips, 2012; Gondi et al, 2019), which corroborates the findings of this study.

Findings suggestive of intracranial hypertension in imaging exams is an extremely valuable resource for the diagnosis of IIH, it has its limitations such as the restriction allowing the visualization of the image only at a certain moment, making continuous monitoring impossible. Furthermore, in order to be realized, it is necessary to transport the patient, which prevents the performance at the bedside. MRI findings suggestive of intracranial hypertension are the empty sella sign, increased CSF, perioptic, tortuosity of the optic nerve and stenosis of the transverse venous sinus (Kohli et al, 2019).

Acetazolamide is currently the first-line treatment due to its ability to reduce the rate of CSF production. Furosemide and topiramate were used as treatment in cases refractory to acetazolamide (Philips, 2012; Bhalla et al, 2019). There was no difference in outcome in patients treated or not with corticosteroids, which corroborates the literature, where there is no recommendation for the use of glucocorticoids for the routine treatment of IIH, being indicated only for severe cases of papilledema that require surgical intervention (Philips, 2012).

This study makes it possible to expand knowledge about this classically uncommon condition in the pediatric population, alerting to the increase in its frequency over the years and identifying some criteria that increase the risk of worse evolution.

5. Conclusion

It is possible to conclude from the study that IIH has become an increasingly important and prevalent differential diagnosis in pediatrics, as well as its early diagnosis. This study presented a demographic profile similar to that presented in the literature, with a higher prevalence of IIH in female adolescents.,

There was a worse evolution in patients with symptoms of blurred vision on admission and a greater risk of needing a surgical approach in patients who had higher CSF opening pressure at the time of diagnosis.

There is an increase in the incidence of this pathology, which implies that it should be considered an increasingly important and prevalent differential diagnosis in pediatrics, since its early diagnosis, in addition to allowing a better quality of life, can prevent severe visual impairment in affected patients.

We encourage researchers to carry out more epidemiological research on IIH to obtain an effective understanding of this patient profile, the behavior of this condition in other regions of the world, so that we can have a better approach aimed at the quality of life of patients.

Limitation

This study has limitations due to the retrospective nature of its analysis, as well as the impossibility of analyzing all patients. Thus, it was not possible to calculate the BMI due to the lack of height data in the analyzed graphs.

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