

Epidemiological study of pediatric patients with signs and symptoms of intracranial hypertension with non-invasive cerebral compliance

Estudo epidemiológico de pacientes pediátricos com sinais e sintomas de hipertensão intracraniana com monitoramento da complacência cerebral não invasiva

Estudio epidemiológico de pacientes pediátricos con signos y síntomas de hipertensión intracraneal con monitorización no invasiva de la distensibilidad cerebral

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Abstract

Introduction: Intracranial hypertension (IH) is a clinical condition secondary to the loss of cerebral compensatory mechanisms. There are distinct methodologies used to diagnose IH and among them is the brain4care (b4c) sensor, which allows non-invasive monitoring of intracranial volume and pressure variations, intracranial compliance. **Objective:** To characterize the epidemiological profile of patients with suspected IH in the pediatric age range. **Method:** A cross-sectional study was carried out in a reference pediatric hospital in Brazil, with patients with signs and symptoms of IH monitored with the non-invasive B4C sensor. The patients underwent neurological evaluation and were submitted to exams - ophthalmological evaluation, lumbar puncture, magnetic resonance imaging (MRI) and computed tomography (CT). **Result:** 58 patients were evaluated, of whom 32 are female (55.2%) and 26 are male (44.8%); most patients presented symptoms such as drowsiness (81%), nausea (77.6%), headache (74.1%), vomiting (63.8%). The ophthalmoscopic examination 77.6% (n=58) of the patients did not show signs of papilledema. On CT and MRI, no changes were found in 84.5% (n=58) and 69.2% (n=26), respectively. Lumbar puncture showed changes in 57.1% (n=21). Considering the interpretation that would be made in adult patients, the b4c sensor monitoring (n=58) showed probable changes in the lying and sitting positions, respectively, in 46.3% and 38.9%. **Conclusion:** It was found that the b4c device can provide a possible complement of clinical information in the process of monitoring cerebral compliance.

Keywords: Intracranial hypertension; Intracranial pressure; Pediatrics.

Resumo

Introdução: A hipertensão intracraniana (HI) é uma condição clínica secundária à perda de mecanismos compensatórios cerebrais. Existem metodologias distintas utilizadas para diagnosticar HI e entre elas está o sensor brain4care (b4c), que permite monitoramento não invasivo do volume intracraniano e das variações de pressão, complacência intracraniana. **Objetivo:** Caracterizar o perfil epidemiológico dos pacientes com suspeita de HI na faixa etária pediátrica. **Método:** Foi realizado um estudo transversal em um hospital pediátrico de referência no Brasil, com pacientes com sinais e sintomas de HI monitorados com sensor não invasivo B4C. Os pacientes foram submetidos à avaliação neurológica e foram submetidos a exames - avaliação oftalmológica, punção lombar, ressonância magnética (RM) e tomografia computadorizada (TC). **Resultado:** foram avaliados 58 pacientes, sendo 32 do sexo feminino (55,2%) e 26 do sexo masculino (44,8%); a maioria dos pacientes apresentou sintomas como sonolência (81%), náusea (77,6%), cefaleia (74,1%), vômito (63,8%). Ao exame oftalmoscópico 77,6% (n=58) dos pacientes não apresentaram sinais de papiledema. Na TC e na RM não foram encontradas alterações em 84,5% (n=58) e 69,2% (n=26), respectivamente. A punção lombar apresentou alterações em 57,1% (n=21). Considerando a interpretação que seria feita em pacientes adultos, o monitoramento do sensor b4c (n=58) mostrou prováveis alterações nas posições deitada e sentada, respectivamente, em 46,3% e 38,9%. **Conclusão:** Verificou-se que o dispositivo b4c pode fornecer um possível complemento de informação clínica no processo de monitorização da complacência cerebral.

Palavras-chave: Hipertensão intracraniana; Pressão intracraniana; Pediatria.

Resumen

Introducción: La hipertensión intracraneal (HI) es una condición clínica secundaria a la pérdida de los mecanismos compensadores cerebrales. Existen distintas metodologías utilizadas para diagnosticar HI y entre ellas se encuentra el sensor Brain4care (b4c), que permite el monitoreo no invasivo de las variaciones de volumen y presión intracraneal y la distensibilidad intracraneal. **Objetivo:** Caracterizar el perfil epidemiológico de los pacientes con sospecha de HI en el rango de edad pediátrica. **Método:** Se realizó un estudio transversal en un hospital pediátrico de referencia en Brasil, con pacientes con signos y síntomas de HI monitoreados con el sensor no invasivo B4C. Los pacientes fueron sometidos a evaluación neurológica y fueron sometidos a exámenes: evaluación oftalmológica, punción lumbar, resonancia magnética (MRI) y tomografía computarizada (TC). **Resultado:** Se evaluaron 58 pacientes, de los cuales 32 son mujeres (55,2%) y 26 son hombres (44,8%); la mayoría de los pacientes presentó síntomas como somnolencia (81%), náuseas (77,6%), dolor de cabeza (74,1%), vómitos (63,8%). El examen oftalmoscópico el 77,6% (n=58) de los pacientes no presentaron signos de papiledema. En la TC y la RM no se encontraron cambios en el 84,5% (n=58) y el 69,2% (n=26), respectivamente. La punción lumbar mostró cambios en el 57,1% (n=21). Considerando la interpretación que se haría en pacientes adultos, el monitoreo del sensor b4c (n=58) mostró cambios probables en las posiciones de acostado y sentado, respectivamente, en el 46,3% y el 38,9%. **Conclusión:** Se encontró que el dispositivo b4c puede proporcionar un posible complemento de información clínica en el proceso de monitoreo de la complianza cerebral.

Palabras clave: Hipertensión intracraneal; Presión intracraneal; Pediatría.

1. Introduction

Monitoring intracranial pressure (ICP) represents essential information for the diagnosis of various clinical conditions, as well as an important clinical evaluation parameter and, often, a determining factor in medical management. The measurement of ICP has been consolidated with invasive techniques, allowing the care of patients with neurological impairment to have a better diagnostic-therapeutic approach, (Rabelo et al, 2021).

Intracranial hypertension (IH) is a secondary condition to the loss of cerebral compensatory mechanisms, leading to an increase in ICP and changes in cerebral blood flow, which can result in brain injury and herniation. Elevated ICP is related to a worse prognosis for patients and is one of the main causes of secondary brain injury in children (Pederson SH et al, 2019). The IH's severity condition shows the need to perform ICP monitoring in a direct and precise manner, allowing for the identification of neurological changes and determining a medical course of action. However, the available methods of monitoring that detect variations in ICP are invasive and associated with potential life-threatening risks (Vilela et al, 2016).

The study of cerebrospinal fluid (CSF) has propelled the definition of the concept of intracranial pressure - pressure resulting within the skull, determined by the balance between the volume of brain tissue, CSF, and blood. This, in turn, recognizing that the skull is a rigid and non-expandable system, served as a foundation for the development of the Monro-Kellie doctrine. This doctrine states that intracranial volume is constant and that the sum of the volumes of blood, cerebrospinal fluid, and brain tissue within the skull must remain stable to prevent an increase in intracranial pressure (ICP). In other words, if there

is an increase in one of these components, the others must adapt to maintain intracranial pressure within normal limits (Moraes FM, et al 2021; Kazimierska et al 1989; Folchini et al 2021).

Although great advances have transformed the history of Medicine with regard to the care of these patients, it is now known that invasive methods of measuring ICP can not only present infectious and hemorrhagic complications that can affect up to 27% of patients submitted to these techniques, but also an inadequate positioning of catheters, that harms clinical evaluation (Moraes FM et al, 2021; Tavakoli S e, et al 2017).

As a result, non-invasive methods of intracranial pressure monitoring have been gaining ground in the last 50 years, not only in terms of establishing the morphology of the intracranial pressure wave, but also in relation to the benefit of continuous monitoring and the longitudinal analysis of trends - parameters that expand the approach to patients in these conditions (Rabelo et al, 2021).

One of the techniques that has been spreading in clinical practice is the evaluation of the increase in the diameter of the optic nerve sheath measured by standardized ultrasound, this technique shown to be accurate and safe because it is not invasive and the possibility of examining patients at the bedside are the main advantages this diagnostic tool, although the main disadvantage is the need for well-trained operators and still not in all hospital centers (Kazimierska et al, 1989; Folchini et al, 2021; Tavakoli et al, 2017; Sujata et al, 2019; De Bernardo et al, 2019).

There is an innovative non-invasive technique that is gaining ground, Brain4care (B4C) is a sensor that responds to variations in intracranial compliance, allowing non-invasive measurement of intracranial pressure, continuous monitoring and prediction of evolution trends. Moraes and collaborators prospectively compared the Brain4care non-invasive sensor with the PIC invasive monitor in 18 adults hospitalized in an intensive care unit with subarachnoid hemorrhage, intracerebral hemorrhage or ischemic stroke and concluded that the new niPCI wave morphology monitor showed good agreement with the standard invasive method and acceptable discriminatory power to detect intracranial hypertension (Sujata et al, 2019; De Bernardo et al, 2019).

Given the current techniques for monitoring intracranial pressure, which are either invasive - such as catheter monitoring or lumbar puncture - or indirect - such as imaging exams - it is necessary to use a safer and more sensitive method to monitor cerebral compliance, Table 1. Thus, the B4C device has the purpose of assisting in the diagnosis with more safety and practicality, reducing the risk of complications and facilitating the immediate diagnosis of minimal cranial deformation.

This study aims to characterize the profile of pediatric patients presenting with signs and/or symptoms of IH and who were monitored non-invasively with the B4C sensor, as well as describe the results of ophthalmoscopy, computed tomography (CT), magnetic resonance imaging (MRI), and manometry.

2. Methodology

This is a cross-sectional study, carried out in an exclusively pediatric hospital of high complexity, located in the south of Brazil. This clinical study protocol was approved by the local Ethics Committee, under CAAE: 42229121.80000.0097, recruitment and occurred during the period from February 2021 to August 2022. Informed consent was obtained from the patients' legal representatives. This work is the first stage of a larger study. The data in this work were extracted from a more comprehensive phase 1 study.

Eligibility criteria for participants

Eligible participants for the study met the following inclusion criteria: both genders, with no restrictions on race, color or social group, aged between 2 years and 17 years, 11 months and 30 days. The following were not included: individuals with recent surgery involving manipulation of the scalp, sedated patients, cranial deformities that prevented sensor placement;

extensive lesions on the scalp, patients with cardiovascular, renal, respiratory and/or rheumatic diseases that could potentially alter non-invasive monitoring.

The study group was composed of individuals with signs and symptoms suggestive of IH (headache, visual changes, nausea, vomiting, irritability, cognitive changes, changes in consciousness, papilledema) evaluated at their hospital admission, where one of the parents or legal guardians consented and signed the Term of Free and Informed Consent (TCLE), as well as the participant consented and signed the Term of Free and Informed Assent (TALE). A total of 58 patients who were admitted to the service with signs and symptoms of IH during the period from 03/01/2021 to 06/30/2022 were included in the study.

All patients admitted to the study group presented signs and symptoms suggestive of Intracranial Hypertension in the pediatric age range. They were properly investigated at primary care and, if necessary, were medically treated for IH symptoms, Figure 1.

It should be noted that according to the evaluation of the responsible pediatrician and according to the patient's severity, in certain cases, the use of the non-invasive monitoring device was only made after the introduction of the necessary supportive measures and stabilization of the patient's symptoms. A period of up to 48 hours after admission was established to perform the monitoring on the patient.

Data Collect

Initially, sociodemographic data and data on IH signs and symptoms were collected, and a description of the variables was performed. The instrument for data collection and storage was CognitoForms, an electronic data capture system, in compliance with the General Data Protection Law (LGPD) and the confidentiality of research. Subsequently, neurological, ophthalmological exams, B4C monitoring, and CT were performed, and if necessary, according to medical evaluation, MRI and measurement of opening/closing lumbar puncture through manometry were performed.

Neurological assessment

The neurological assessment it was performed only by a single researcher, to avoid possible examiner bias. And, it evaluated the presence or absence of signs and symptoms that referred to changes in ICP, such as changes in the level of consciousness, headache, vomiting, nausea, visual changes, drowsiness, drop in school performance, inattention, irritability, dizziness, seizures. Subsequently, the same professional evaluated the details of the neurological examination, Glasgow coma scale, pupillary reflexes and other cranial nerves, graduation of muscle strength and osteotendinous reflexes, static and dynamic balance and data on motor coordination, in addition to the presence or absence of signs Meningeal and cranial deformities.

Criteria Diagnostic HI

The diagnosis criteria of intracranial hypertension in this study were the combination of clinical data, ophthalmoscopy, and the results of complementary CT, magnetic resonance imaging (MRI), and lumbar puncture with manometry. Data from monitoring with the B4C device were not considered for the diagnosis of IH in the participants, Figure 1.

Use of non-invasive sensor for monitoring and interpretation of curves and their parameters associated with intracranial compliance

This method, B4C, is based on the principle of detecting nanometric expansions on the outer surface of skull bones caused by changes in ICP. The device is attached to a headband with a certain tension, the sensor pin has surface contact with the head and keeps the device in the frontotemporal region. The bone deformations caused by alterations in the PIC, are translated by the positioning on the pin that bends the internal cantilever beam of the sensor that captures these alterations in the blade

through a set of extensometers, Figure 2, (Andrade et al, 2021). Non-invasive monitoring of each patient occurred in two positions, with a period of five minutes in each position. In the first moment, the patient was in the lying position 0° and in the second moment in the sitting position with an inclination of 45° , both for up to five minutes. The sensor can collect, filter, amplify and digitize the monitored signal and issue a report with associated parameters minute by minute.

When the signal from the sensor used in the noninvasive device is plotted, the resulting curve is very similar to that obtained using invasive ICP monitoring. The pulse pressure curve is subdivided into three waves: P1 — the percussion wave, which is related to the arterial pulse transmitted to the choroid plexus and is usually the largest peak; P2 — the tidal wave, which is related to the compliance of brain tissue; and P3 — the dicrotic wave. Final compliance is given by the ratio $p2/p1$, (Andrade et al, 2021).

After the ICP had been monitored, the software saved the data in files that were subsequently loaded into the Braincare® system for analysis the result is a report containing the P2/P1 ratio. The P2/P1 ratio assesses intracranial compliance and was defined as the ratio between the amplitudes of P2 and P1 peaks ($R = \text{AmpP2}/\text{AmpP1}$). Non-invasive monitoring data were obtained by analyzing the morphology of the ICP waveform (Andrade et al, 2021).

Based on studies carried out with the device in adults, the interpretation of the P2/P1 ratio and its values, in this adult population, is as follows: values >1.2 are suggestive of changes in compliance; values between 1 and 1.2 may be related to changes in compliance and suggest greater observation in the patient, and values between 0.65 and 1 are considered normal, (Andrade et al, 2021).

Statistical analysis

Statistics were conducted by an independent professional. Results for quantitative variables were described by means, medians, minimum values, maximum values, and standard deviations. Qualitative variables were described by frequencies and percentages. Data were organized in an Excel® spreadsheet and analyzed with the Stata/SE v.14.1 StataCorp LP, USA computer program.

3. Results and Discussion

Fifty-eight patients were evaluated, of which 32 were female (55.2%) and 26 were male (44.8%), table 2. A portion of 35 patients (60.3%) had pre-existing diseases, of which 32 (55.2%) had neurological diseases. The main symptoms described were drowsiness (81%), nausea (77.6%) and headache (72.2%), followed by vomiting (63.8%) and dizziness (53.4%), table 3. Neurological examination was normal in 81.5 % of the patients, with the suspicion of IH being primarily of a clinical nature and on ophthalmological examination 77.6% of the children did not reveal the presence of papilledema.

The results of the cranial CT scan did not show alterations suggestive of IH in 84.5% of the cases. In the patients who underwent cranial MRI examination, signs of IH were ruled out in 69.2% of the cases.

Of the 21 patients who underwent CSF puncture, the median opening pressure was 27 mmHg with variations from 9 to 49 mmHg and 60.3% of the cases had manometry values above 20 mmHg.

The B4C sensor showed altered P2/P1 ratio in the lying position in 46.6% of patients and altered P2/P1 ratio in the sitting position in 41.4% of patients. IH was confirmed, through the standardized criteria considered in this study, in 23 of 58 patients. It should be noted that in this work the B4C was not used for diagnosis and clinical management.

This is the first study in the literature evaluating the epidemiological data of children with signs and symptoms of IH monitored with the non-invasive B4C device. The non-specificity of clinical data in the final diagnosis of intracranial hypertension and the diversity of clinical manifestations in different patients are known (Aylawar et al, 2018).

It is pointed out that papilledema - one of the main clinical signs for predicting the presence of IH - is defined as edema of the optic disc caused by increased pressure inside the skull. The literature shows us that the sensitivity of papilledema in IH situations varies from 14% to 40% (Nazir et al, 2009).

The study showed us that 40% of patients with suspected optic disc edema were diagnosed with pseudoedema. Such data corroborates those found by the authors in the present study, since the ophthalmological examination did not show changes in most patients submitted to this evaluation (72.2%). This shows that, although fundoscopy is an integral part of the neuro-ophthalmological examination, there are still obstacles in the diagnosis of IH based on the absence of papilledema (Carta et al, 2012).

As for the main signs and symptoms found by the authors and described in the results section, the findings converge with those described in the literature, as cited by Aylward and collaborators¹¹ in a review about intracranial hypertension in pediatric patients. Furthermore, another study describes the same clinical signs as initial findings in intracranial hypertension syndromes (Aylawar et al, 2018; Tadevosyan et al, 2021).

Besides the potential non-specificity of clinical signs, existing non-invasive complementary tests to aid in the confirmation of IH may demonstrate only indirect and suggestive signs of the condition, as is the case with CT. The findings that indicate IH on CT are obliteration of mesencephalic cisterns, blurring of white matter and brain ash, loss of subarachnoid space, and ventricular compression (Giugno et al, 2003). According to literature, CT radiological findings have no predictive value for the course of IH (Rosenberg et al, 2011).

In addition, the use of CT is indicated mainly for chronic cases of IH, since in acute cases the changes may not always be present (Nazir et al, 2009). This is consistent with the results of this study, since 84.5% of patients undergoing CT showed no changes. Therefore, it is worth noting that a CT image without alterations does not rule out IH (Jeng et al 2019).

As for MRI, the findings suggestive of intracranial hypertension are the empty sella sign, released periodic CSF, optic nerve tortuosity, transverse venous sinus stenosis, and altered signal between neurohypophysis and adenohypophysis, all of which are indirect findings. In our study, 69.2% of patients submitted to MRI did not present alterations compatible with IH (Chen et al, 2021).

From the data obtained, the authors found evidence that the clinical examination alone was not sufficient to support the diagnosis of intracranial hypertension on a solid basis, and negative results of ophthalmoscopy, skull CT, and MRI do not rule out the presence of IH (Behrens et al, 2011).

Thus, in this research, all patients who underwent lumbar puncture and those who obtained values of opening pressure above 20mmHg in the manometer were automatically considered with a diagnosis of IH. The reference used by the authors as criteria for the cutoff value of the manometric opening pressure was the study conducted by Behrens et al in 2010.

The literature shows a study of non-invasive monitoring through the B4C that was developed by Ballestero, in 2017, which discussed the analysis of the behavior of the non-invasive device in 28 pediatric patients with hydrocephalus. The authors concluded that the device generated curves that can be evaluated in clinical practice to measure intracranial compliance. These results seem promising, although in this study, the authors did not intend to analyze the P2/P1 ratio values.

Exactly because of the difficulties presented above in detecting the final diagnosis of IH through non-invasive tests, which are used in medical routine, the B4C device presents us with a 100% non-invasive proposal for potential monitoring of intracranial compliance.

In addition, the portability of the device and the possibility of using it at the bedside allows for serial monitoring in places that are difficult to reach, such as intensive care units (ICU).

The pediatric profile of this study included patients with suspicion of IH from the onset of symptoms to final diagnosis and reveals that the diagnostic journey is challenging for medical professionals. Complementary exams are important tools; however, they often show only indirect signs of IH, and patients may need to undergo invasive procedures for a definite diagnosis.

Limitations

The study found some limiting factors regarding the device. The sensor is sensitive to movements, however small they may be, such as blinking, closing and/or mouth opening, as well as the use of a pacifier and even external sounds such as crying. Therefore, in order to obtain good quality monitoring, the pediatric patient needs to be relaxed. No type of sedation was used, as some medications influence intracranial compliance values.

Another limitation found was the number of participants, since the recruitment period took place during the Covid-19 pandemic and global health limitations, which made it difficult for us to access the patient.

Being a cross-sectional study, there are relevant limitations of this method, not being possible to establish cause and effect relationships between a condition and its risk factors. Data reported in the study are imminently epidemiological, being part of a larger study. And, limitation of a single medical evaluator.

4. Conclusion

In an unprecedented way, this study describes the epidemiological profile of pediatric patients with signs and/or symptoms of IH, revealing that the patient's journey to diagnosis is challenging for the medical team.

Monitoring intracranial compliance with a non-invasive B4C device represents a potential alternative for patients with signs and symptoms of IH. B4C also allows for easy, serial monitoring, making it a portable option for locations where complementary exams are difficult to access. Therefore, the present authors suggest that this study may be a starting point for further research on the sensitivity and specificity of the diagnostic tests available for IH in pediatrics, in order to better understand intracranial compliance and the actual clinical use in pediatric patients with suspected IH.

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