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Original Article

Secondary Intracranial Hypertension in Pediatric Patients With Leukemia

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ABSTRACT

BACKGROUND: We investigated the clinical characteristics of a pediatric population with hemato-oncological disease and intracranial hypertension, analyze the therapeutic response and outcome, and compare its characteristics with respect to a control group with idiopathic intracranial hypertension. **METHODS:** We retrospectively analyzed patients with hemato-oncological disease and secondary intracranial hypertension in our center during the past five years. We compared these individuals with a historical cohort with idiopathic intracranial hypertension from our institution (control group). **RESULTS:** We identified eight patients, all with leukemia, and 21 controls. Mean age at diagnosis was 10.6 years, and 62% of individuals were female. Most of them were under treatment with drugs (62% corticosteroids, 75% active chemotherapy). Mean opening pressure of cerebrospinal fluid was 35 cm H_2O. All had headache, but only 28% complained of visual symptoms. Only 12.5% exhibited papilledema at the time of diagnosis (versus 71% in controls). All of them were treated with acetazolamide, with average therapy duration of nine months, and all had a favorable outcome (versus 57% of controls who needed second-line treatment). None of them showed long-term visual complications (versus 20% of controls). **CONCLUSIONS:** Patients with hemato-oncological disease and secondary intracranial hypertension may not develop typical symptomatology. Thus, diagnosis and recognition of this entity among this cohort may be difficult. Associated factors are diverse and do not show an obvious causal relationship. A high index of suspicion must be maintained for diagnosis, because a favorable outcome is expected with prompt treatment. Acetazolamide is effective as a first-line therapy and caused few side effects.

Keywords: acetazolamide, idiopathic intracranial hypertension, leukemia, papilledema, pseudotumor cerebri, chemotherapy; secondary increased intracranial pressure

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Introduction

Idiopathic intracranial hypertension (IIH) refers to the elevation of the intracranial pressure in the absence of a mass lesion, ventriculomegaly, or underlying central nervous system infection. When there is a likely explanation for the increased intracranial pressure, the term secondary intracranial hypertension (SIH) is preferred; otherwise, the term primary idiopathic intracranial hypertension is used. The older term "pseudotumor cerebri" encompasses both IIH and SIH in one single term.

IIH is uncommon in childhood. A recent population-based study from the United States estimated an annual

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incidence of IIH and SIH of 0.63 and 0.32 per 100,000 children, respectively.[1] Previous prospective studies placed the incidence at 0.9-2.36 per 100,000, even as high as 15 to 19 per 100,000 in obese population of childbearing age.[2-5] It is often characterized by the presence of headache, vomiting, dizziness, tinnitus, or visual disturbances. Neurological examination must be normal except for the possible discovery of optic disc edema or a false-localizing sixth nerve palsy.

A definite diagnosis of IIH requires the demonstration of an increase in the opening pressure of the cerebrospinal fluid (CSF) on lumbar puncture, in the absence of underlying vascular or structural abnormalities, and a normal CSF composition.[6-8] Current guidelines allow different pressure measurements, but a threshold opening pressure of greater than 25 cm H_2O is usually accepted as abnormal for children as traditionally suggested by the Modified Dandy Criteria in adults, lowering it to 18 cm H_2O for children less than age eight years.[6-12] The Idiopathic Intracranial Hypertension Treatment Trial accepts 20 cm H_2O as the cutoff value, in the presence of a sixth nerve palsy, pulse-synchronous tinnitus, at least grade 2 papilledema, or transverse sinus stenosis or collapse on neuroimaging.[11] The Friedman criteria suggested a threshold greater than 28 cm H_2O for children, based on pediatric series suggesting higher mean opening pressure values. There is still debate about the normal CSF opening pressure, in part because some of these earlier studies included patients with demyelinating and white matter disease as controls, and their pressure readings may have falsely elevated the average opening pressure.[7,8,13] Normative values for children are not well established because normal sampling of pediatric patients is difficult because of ethical considerations, but application of stricter criteria may result in missed cases and potential morbidity.

The pathophysiology of an increased CSF opening pressure remains unknown, although it might relate to a disturbance in the CSF production-reabsorption dynamics.[14] Secondary causes that have most often been associated with this condition are various autoimmune and endocrine disorders (such as systemic lupus erythematosus, sarcoidosis, hypoparathyroidism, Addison disease, or Behcet disease), chronic infections, and drugs (including corticosteroids, antibiotics, immunosuppressants, and chemotherapeutic agents),[7,15] which could be responsible for Na^+/K^+ pump dysfunction at the arachnoid granulations.[16] Anemia, oxidative stress, and hypercapnia are associated with increased brain capillary permeability.[17]

The evaluation of children with headache and signs of increased intracranial pressure represents a major challenge because of the wide range of diagnostic possibilities.[7] This assessment can be even more complicated in children with an underlying hemato-oncological disease, in whom the occurrence of acute headache may incur a thorough differential diagnosis. Various diseases and treatments have been described to predispose hemato-oncology patients to intracranial hypertension.[15] However, its diagnosis is often overlooked because the presenting features do not always meet the usual clinical criteria.[15]

The aim of our study was to analyze the clinical features of a pediatric population with an underlying hemato-oncological disease who developed elevated intracranial pressure and to compare these individuals with our institution's IIH controls.

Methods

We reviewed the medical records of children with underlying hemato-oncological disease diagnosed with SIH over the past five years (2009 to 2014) belonging to the Hematology-Oncology Section of the University Children's Hospital Niño Jesus in Madrid (Spain), a tertiary referral hospital for pediatric patients with hemato-oncological disease. In addition, we carried out a retrospective review of medical records of children diagnosed with IIH in a ten year interval (2004 to 2014) in the neurology section of the same center to establish a historical cohort as control group for the comparative cohort study.

Inclusion criteria were patients with clinical signs of intracranial hypertension (headache, nausea, vomiting, visual disturbances, papilledema) and increased CSF opening pressure measured, taking reference cutoff values above 25 cm H_2O, according to the modified criteria proposed by Dandy and Friedman,[6-8] with normal neuroimaging and cytochemical study of CSF, and unaltered neurological examination (except for the presence of optic disc edema or abducens nerve palsy). Patients without a diagnostic opening pressure, according to those reference values, who had a dubious elevation between 20 and 25 cm H_2O but fulfilled other clinical criteria, were also considered. Opening pressure was measured by lumbar puncture, which according to our institution protocols was performed in all of our patients under light sedation conditions (cutaneous anesthetic patch and buccal midazolam), all of them awake, and in a lateral decubitus with semiflexed legs positioning.

The following data were collected from all cases: age at diagnosis, sex, height and weight, underlying disease and comorbidities, presenting symptoms of IH (headache, vomiting, visual disturbances), hemoglobin (Hb) levels at diagnosis, cytochemical composition of CSF, CSF opening pressure, ocular fundus findings, treatment received, side effects, need for second-line treatment, and outcome. All patients underwent brain imaging by magnetic resonance imaging (MRI). MRI was performed at our center on a 1.5-T system that included T1, T2, and diffusion conventional sequences, including venous angiography.

All procedures performed were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments. For this type of study, given its retrospective nature, formal consent was not required.

Main findings

Following our inclusion criteria, we obtained data from eight patients with hemato-oncological disease (all with leukemia) with SIH, considered our study group, and 21 patients with IIH, considered our control group. Average age at diagnosis in the hemato-oncological disease group was 10.6 years (equal to the average age of the control group, with an age range from four to 16 years). In both groups, there was a female preponderance (62%). Regarding comorbidities and associated risk factors, only one individual (12.5%) was overweight (body mass index greater than 25) in the hemato-oncological disease group, whereas that amount rose to 43% in the control group. Possible etiologies or associations found in the group of patients with hemato-oncological disease were a positive history of recent medical treatments in all of them, with up to 62% of cases with corticosteroid intake (over the previous month or on a withdrawal regimen) and up to 75% receiving chemotherapy at the time of diagnosis. The spectrum of diseases included B-type acute lymphoblastic leukemia (the most frequent form, 75%), T-type acute lymphoblastic leukemia (12.5%), and acute myelogenous leukemia (12.5%).