Intracranial Hypertension in a Child with Turner Syndrome Receiving Recombinant Human Growth Hormone

Hipertensão Intracraniana em Criança com Síndrome de Turner Tratada com Hormona de Crescimento Recombinante

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ABSTRACT

We report for the first time in a Portuguese child a case of intracranial hypertension (ICH) in a girl with Turner syndrome under hormonal therapy with recombinant human growth hormone (rhGH).

A fourteen-year-old child with Turner syndrome medicated with estrogen and rhGH 1.6 mg/daily for 3 years followed regularly at our Pediatric Department presented with diminished vision. Myopia was diagnosed and corrected, and her best corrected visual acuity was 10/10 bilaterally. Funduscopic exam showed bilateral hyperemic optic nerve edema, confirmed by optical coherence tomography (OCT). Cranial computer scan tomography (CT) and head magnetic resonance imaging (MRI) did not show any alterations. The child was then referred to Neuropediatrics Department. Lumbar puncture revealed elevated intracranial pressure, confirming the ICH diagnosis. rhGH was discontinued.

ICH is a rare condition in the pediatric population. There is a causal relationship between rhGH therapy, Turner syndrome and ICH development. To our knowledge this is the first Portuguese case report of this association. As ICH could potentially lead to irreversible vision loss, children receiving rhGH should have a routine follow-up by ophthalmology.

KEYWORDS: Child; Human Growth Hormone/adverse effects; Human Growth Hormone/therapeutic use; Intracranial Hypertension/chemically induced; Turner Syndrome/drug therapy

RESUMO

Apresentamos um caso clínico de hipertensão intracraniana (HIC) numa criança com síndrome de Turner sob tratamento com hormona do crescimento (HC).

Criança de 14 anos com síndrome de Turner sob terapêutica hormonal com estrogénio e hormona de crescimento (1,6 mg/dia) apresentou-se no serviço de urgência por diminuição da acuidade visual. A fundoscopia revelou edema bilateral da papila, confirmada por tomografia de coerência ótica (OCT). A tomografia computorizada e a ressonância magnética cerebrais não revelaram quaisquer alterações. A criança foi referenciada ao departamento de Neuropediatria. Realizou-se

punção lombar que revelou aumento da pressão intracraniana e, desta forma, fez-se o diagnóstico de HIC. Optou-se pela suspensão da hormona do crescimento.

A hipertensão intracraniana é uma entidade rara na população pediátrica. Há uma relação causal entre o HIC, o tratamento com hormona do crescimento e a síndrome de Turner. Do nosso conhecimento, é o primeiro caso em Portugal que descreve esta associação. Dado que a HIC pode levar a perda irreversível da acuidade visual, todas as crianças sob terapêutica hormonal com hormona do crescimento devem ser avaliadas de forma rotineira por oftalmologista.

PALAVRAS-CHAVE: Criança; Hipertensão Intracraniana/induzida quimicamente; Hormona de Crescimento/efeitos adversos; Hormona de Crescimento/uso terapêutico; Síndrome de Turner/tratamento farmacológico

INTRODUCTION

Idiopathic intracranial hypertension is defined by clinical criteria as an elevated intracranial pressure (over 240 mm H2O) with normal cerebrospinal fluid (CSF) composition documented by lumbar puncture in the absence of mass, deformity, displacement or obstruction of the ventricular system documented by computed tomography and magnetic resonance imaging.[1]

The usual presenting symptoms include headache, nausea, vomiting, transient obscurations, double or blurred vision and stiff neck. In adolescents the most common symptom is headache that usually takes upon an organic cause.[2]

In pediatric population, ICH is associated with endocrine abnormalities, medications, viral infections, nutritional deficiencies or systemic conditions whereas recombinant human growth hormone (rhGH) therapy and Turner syndrome are included.[3]

The rhGH is available from 1985 and is actually approved for the idiopathic GH deficiency, Turner syndrome, Prader-Willi syndrome, delayed puberty and empty sella turcica syndrome.[4] It is considered a safe therapeutic option but there are some adverse effects described, such as insulin resistance and ICH which is the earliest side effect and can affect 0.1% to 0.2% of patients receiving rhGH.[5]

Turner syndrome by itself increases the risk of ICH development due to misregulation in the estrogens and progesterone hormonal balance.[6]

We report, for the first time in Portugal, a case of ICH in a girl with Turner syndrome diagnosed three years after starting rhGH therapy. Her mother has given her written informed consent to publish the case.

CASE REPORT

A fourteen-year-old girl with Turner syndrome, followed regularly at our Pediatric Department, presented for a routine observation after complaining of diminished vision for far. She denied any accompanied symptoms such as headache, nausea or vomiting. She was under estrogen and rhGH (1.6 mg/daily) replacement therapy for 3 years. Her height was 140 cm, her weight was 47.2 kg and her body mass index (BMI) was 24.1 kg/m^2.

On ophthalmological examination, myopia was diagnosed and corrected, and her best corrected visual acuity was 20/20 bilaterally. Pupillary reflexes were unremarkable, with no afferent pupillary defect. Extra-ocular movements were unimpaired. Intraocular pressure was 13 mmHg in the right eye and 14 mmHg in the left. Funduscopic exam showed bilateral hyperemic optic nerves edema, confirmed by optical coherence tomography (OCT) without any macular alteration. Color vision tested via Ishihara plates showed no defects in either eye.

Standard automated perimetry (SAP) revealed unspecific peripheral visual defects with mean defect (MD) of 9.3 dB in her right eye and of 7.7 dB in her left.

An urgent cranial computer scan tomography (CT) was ordered and showed normal ventricular size without any evidence of mass, hemorrhage, edema or ventricular compression. Head magnetic resonance imaging (MRI) did not show any alterations.

Intracranial hypertension was suspected, and the child was then referred to Neuropediatrics Department. There were no focal signs of neurologic disorder. Lumbar puncture revealed an opening pressure of 310 mmH2O with normal cerebrospinal fluid (CSF) composition. Due to this elevated intracranial pressure and the absence of intracerebral morphological lesions, the diagnosis of ICH was confirmed. rhGH was discontinued, no additional therapy was prescribed, and she has been kept under close follow-up. They refused to stop estrogen therapy. Her visual symptoms gradually improved and optic disc edema restored one year after rhGH discontinuation.

DISCUSSION

Idiopathic ICH is defined as an elevation of intracranial pressure with normal CSF composition in the absence of intracranial morphological alterations. The annual incidence is 1 in 100 000 people over general population and can be caused by a variety of underlying conditions.[7] Turner syndrome and recombinant human growth hormone replacement therapy are included. ICH is a rare but significant side effect of rhGH therapy.[8]

In pediatric population, the most common symptom is intractable headache that worsens in lying down position and is usually accompanied by nausea and vomiting. Although rarely, children could present with no headache as

in our case.[9]

The visual acuity is not usually much impaired. Relative afferent pupillary defect and diplopia due to sixth nerve palsy may occur.[2] Fundoscopic examination reveal hyperemic optic nerves edema, confirmed by OCT.

Visual fields often show enlargement of blind spot. In our patient, we found peripheral visual field defects, but we assume them as inconclusive due to lack of cooperation and poor reliability indexes even in a second effort to perform the exam.

Turner syndrome (TS), the most common chromosomal disorder in woman, results from the partial or complete absence of one of the X chromosomes. Short stature, ovarian dysgenesis and failure are the most prevalent abnormalities. Growth hormone and steroid replacement therapy enhances the growth, pubertal development and quality of life.[10] TS itself increases the risk for ICH due to estrogen and progesterone deficiency. However, in these patients, the ICH is more probably related to rhGH replacement therapy.

The association between rhGH and ICH was first reported by Otten et al in 1992. It has been increasingly reported due to higher doses and larger periods of treatment and it is estimated to affect 1.2 in 1000 children receiving rhGH with a mean age of incidence of 9 years.[5] It is known that rhGH-induced ICH is dose related but there is not known the specific dose that increases the risk. However, Malazonski and Koller found that most cases occur with a dosage ranging from 0.17 to 0.35 mg/kg per week.[11] The onset of symptoms is thought to occur one week to five years after initiation, but usually within days.[12] In our case, the dose (0.24 mg/kg/week) was in the range but the symptoms started 3 years after starting the therapy. It is very uncommon and to our knowledge there are very few cases reporting this delayed side effect. GH-induced ICH may result from increased CSF production by the choroid plexus due to increase of GH in CSF that induces both local production of insulin growth factor 1 (IGF-1) and activation of its receptors.[13] Alternatively, sodium and water alterations mediated by stimulation of renin-angiotensin system may play a role, in particularly in patients with renal impairment.[14]

Idiopathic ICH usually goes until spontaneous remission. However, persistent headache or progressive visual loss deterioration due to optic nerve involvement are indications for treatment.[15] The cornerstone of treatment directs to underlying conditions, most of times with cessation of any drug thought to have precipitated.[16] Medical treatment includes the use of diuretics, in particular acetazolamide. Patients who do not respond to medical therapy, should go under therapeutic LP or more aggressive techniques such as cerebrospinal fluid diversion procedure or optic nerve fenestration. We decided to withdraw rhGH and not to start additional therapy due to good visual acuity and lack of objective optic nerve damage. However, we explained to the mother that we might have to start acetazolamide if there was no clinical improvement. Fortunately, there was clinical improvement ant to our knowledge this is the first case with clinical recovery without any medical or surgical treatment.

In the majority of patients, resolution of papilledema and symptoms takes 3 to 6 months. In our case, it took one year but it could be justified by the fact that we did not prescribe diuretics.

The neuropediatrician decided not to reintroduce the rhGH.

CONCLUSION

ICH is a rare condition in the pediatric population. There is a causal relationship between rhGH therapy, Turner syndrome and ICH development.

To our knowledge this is the first reported case with clinical improvement without additional therapy and one of the few reporting this rare side effect years after.

All children receiving rhGH should have regular and careful neurological and ophthalmological examinations as ICH could be naked of symptoms. Although the prognosis is usually favorable, ICH could potentially lead to irreversible vision loss if not recognized and treated early. Our case emphasizes the need of a close collaboration between pediatricians, endocrinologists and ophthalmologist in these patients.

RESPONSABILIDADES ÉTICAS

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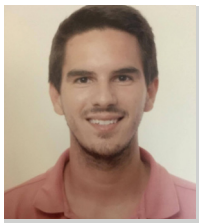

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