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Case Report

Approach to Chronic Secondary Headache: A Case Report on Unusual Drug Side Effects

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Abstract

In this article, we present the case of a 12-year-old female child who complained of bilateral temporal and frontal headache for 2 to 3 months with nausea and vomiting. Physical examination revealed right-sided sixth cranial nerve palsy and papilledema in ophthalmoscopy. To find the cause of increased intracranial pressure, the patient underwent brain imaging and brain MRI showed no abnormality. Ultimately, lumbar puncture (LP) was performed and cerebrospinal fluid (CSF) pressure was 280 mmH_2O with normal chemistry. We considered pseudotumor cerebri as the first diagnosis. LP was carried out three times and 30cc of CSF was tapped each time. Finally, patient's headache and papilledema improved and physical examination after 6 months showed no sign of raised intracranial pressure (rICP). The most prominent point in her past medical history was the use of growth hormone (GH) for 2 years. No sign of symptom relapse has been seen after 6 months of drug discontinuation. We must consider the hazard of growth hormone as a potential cause of increased intracranial pressure. When the use of GH is justified, the follow-up must include an ophthalmoscopy examination in each session.

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What's Known

- Most common complaint in children is nervous headache.
- In children's nervous headache, if focal signs are observed, eye examination and review for increased intracranial pressure are essential.

What's New

- Rare side effects of drugs are often associated with nervous headache in children.
- After physical examination and neuroimaging in neurological diseases in children, attention to drug illustrations, especially when the drug is used for a long time, is necessary.

Introduction

Headache is a common complaint in children and adults. The most important causes of primary headache are migraine, tension type, trigeminal autonomic cephalgia, and cluster headache. The secondary causes of headache are trauma, vascular and non-vascular injury, infection (meningitis, sinusitis, teeth, nose, mouth, drug, etc.).[1] Headache in children can lead to reduced school performance and social dysfunction. Thus, diagnosis and treatment of the underlying cause in patients with headache is important.

Growth is a biological process, which may be affected by genetic, nutritional, environmental, and hormonal factors. A growth rate of 2 SD below the mean normal cure is abnormal and the underlying causes must be investigated, which may include systemic diseases, nutrition, emotional factors, endocrine diseases (hypothyroidism, GH deficiency), chromosomal abnormalities, dysmorphic diseases, metabolic causes, etc. Somatotropes cells of the pituitary gland secrete growth hormone whose secretion continues throughout life, although varies based on growth period of humans. GH is used as a therapeutic agent in

a variety of situations, including GH deficiency, Turner syndrome, chronic renal failure before transplantation, small-for-gestational age short stature, and idiopathic short stature, including osteogenesis imperfecta and Sanjad-Sakati syndrome,[1] Noonan syndrome, SHOX gene abnormality, and Prader-Willi syndrome.

Generally, growth hormone is a safe drug in children.[2] During treatment with growth hormone, the risk of type 2 diabetic mellitus increases 6-fold (no effect on type 1 diabetic mellitus).[3] Recurrence of a brain tumor, leukemia, and other neoplasms has not been reported, but there is no established report of recurrent of neoplasm in patients who use recombinant human growth hormone.[4] There is no report of Creutzfeldt-Jakob disease after using recombinant human GH either.

Idiopathic intracranial hypertension (IIH) is a syndrome with high intracranial pressure that usually occurs in obese women during the reproductive years.[5] Patient maintenance in an alert and oriented mental state without localizing neurologic finding are the signs and symptoms of IIH. There are no signs of deformation or obstruction of the ventricular system and neurodiagnostic studies are otherwise normal except for an increase in cerebrospinal fluid pressure.[6] Studies have shown that the annual incidence of IIH in the Western world is about 0.9/100,000 persons and 3.5/100,000 in females aged 15 to 44 years.[7] However, it can vary depending on location.

Raised ICP and increased intraocular pressure is a rare complication of treatment with GH and thyroid.[8] Raised ICP (rICP) is a neurological syndrome and is divided into primary (idiopathic) and secondary forms. A summary of epidemiological studies on IIH reported different rICP prevalence (e.g., 1.7 in Libya,[9] 0.9 in USA,[7] 0.03 in Japan,[10] 1.57 in UK,[11] and 0.28 in Italy[12] per 100,000/year). Other reported side effects of GH therapy are dislocation of epiphyseal femoral head, worsening of preexisting scoliosis, pancreatitis, transient gynicomasty, and novus hyperpigmentation with overgrowth and increased risk of hemorrhagic stroke.[5,13-15]

Stroke, carpal tunnel syndrome, edema, and arthralgia are commonly seen in adults treated with human growth hormone but are uncommon in children. The aim of this study is to determine the importance of follow-up in patients who receive GH.

Case Presentation

We present a 12-year-old girl whose chief complaint was frontotemporal headache with nausea, vomiting, blurred vision, and transient diplopia since 2 months before admission. Permission and written consent were obtained before treatment. She had been treated for GH deficiency (administer growth hormone, 0.2 mg/kg/week) since 2 years ago. She also had hypothyroidism and was under treatment (levothyroxine in a dose of 50 µgr daily) for 5 years. Headaches had worsened on wake up and in the evenings. She was referred to a neurologist. The result of physical examination (P/E) was papilledema on ophthalmoscopy and right-sided sixth cranial nerve palsy. There was no sign of neck stiffness. Imaging study was performed and the brain MRI showed no abnormality. Figure 1 shows a normal signal intensity of cerebral hemispheres. The deep white matter structures were normal. Cerebral ventricles were normal and no midline shift and hydrocephalus were noted. The posterior fossa, including cerebellum and 7th-8th nerve root complexes were normal. Lumber puncture (LP) was done that indicated CSF pressure of 280 cmH2O with normal biochemistry (table 1). During 2 months, CSF was taped three times (25cc each time) while GH use was discontinued. At the 2-month and 6-month follow-up, all symptoms and signs (headache, blurred vision, papilledema, and diplopia) were relieved.

Discussion

ICP rise as a complication of drug use is not uncommon. Physiopathology of rICP after using a series of drugs is obvious (rICP as a complication of oral contra captive (OCP) because of cerebral venous thrombosis). However, physiopathology is not evident in most cases (idiopathic).

The use of growth hormone has increased in our society due to the increased survival of syndromic patients with short stature and the importance of starting treatment before puberty. Therefore, there is a need for adequate

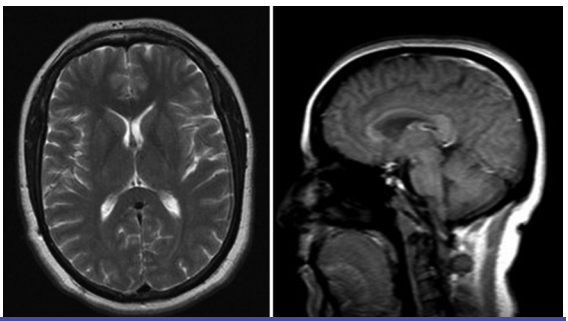

Figure 1: Normal signal intensity of cerebral hemispheres. The deep white matter structures are normal. Cerebral ventricles are normal and no midline shift and hydrocephalus are noted. The posterior fossa including cerebellum and 7th-8th nerve root complexes are normal.

Table 1: Laboratory and physical examination data of the patient

CBC: Hematology	Thyroid function test	CSF analysis	Biochemistry	P/E
WBC: 8.2	T3: 2.0	Protein: 31	Blood sugar: 163	Weight=40 Kg
RBC: 4.75	T4: 9.4	Sugar: 64	Urea: 35	PR=74
Hemoglobin: 12.5	T.S.H: 2.1	RBC: Not seen	Creatinine: 0.8	RR=18
Hematocrit: 37.8		WBC: 3	Ca: 10.1	HT=125 cm
MCV: 79.6			Na: 141	BP=120/73 mmHg
MCH: 26.3			K: 4.2	
MCHC: 33.1				
PLT: 276				

WBC: White blood cell; RBC: Red blood cell; MCV: Mean corpuscular volume; MCH: Mean corpuscular hemoglobin; MCHC: Mean corpuscular hemoglobin concentration; PLT: Platelet; T.S.H: Thyroid stimulating hormone; PR: Pulse rate; RR: Respiratory rate; HT: Height; BP: Blood pressure

information on rare complications of growth hormone drug. Our patient had received both the growth hormone and levothyroxine drugs, which were the cause of rICP. Levothyroxine drug has been used in the past 5 years with no rICP side effects. However, our patient additionally took the growth hormone for two years that caused rICP complication. Consequently, by discontinuing the second drug, complications along with side effects disappeared. Hence, there is no need to remove the levothyroxine drug and patients can continue treatment without rICP.

Idiopathic rICP has been reported in several studies and also as a complication of a list of drugs, including chlordecone (kepone), ketoprofen or indomethacin in Bartter's syndrome, thyroid replacement therapy in hypothyroid children, tetracycline and its derivatives, amiodarone, hypervitaminosis A, lithium carbonate, nalidixic acid, sulfa antibiotics and risperidone.[5] There are situations (risk factors) which increase the risk of rICP as a complication of the above-mentioned drugs. More important risk factors are obesity, weight gain, endocrine disease (Addison's disease, hypoparathyroidism, steroid withdrawal,[16] and growth hormone therapy in children).[5]

Wall[17] (2008) reported that around 60% of patients were above 10 years of age and it was more prevalent in females. Bruce et al.[18] studied 197 black and 253 white patients with increased intracranial pressure. They showed that rICP was more in black than white patients and associated with the loss of vision in one eye.

The most common sign in P/E in patients who are treated with GH prepubertal is diplopia because of the sixth nerve palsy secondary to rICP. Visual field defect is seen in 13-38% of patients, especially in prepubertal age.[19] The neurologic and complete eye examination are necessary, especially in syndromic children (Turner, Down, Noonan, and psychotic patients) since these groups of patients cannot declare their problems to their family. Moreover, physicians do not usually pay attention to their speech (regarding delusional aspects of psychotic disorders). As for Turner syndrome, ophthalmoscopy is recommended prior to treatment.[19] Moreover, treatment with acetazolamide can be used in refractory patients to lumbar puncture.[16,17,19]

Conclusion

Rising of ICP is not uncommon complication of drug on long-term use. In case it remains unnoticed during patient follow-up, it can result in untreatable complications. We recommend routine ophthalmoscopy and eye movement examination in each session of patient exam.

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