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Case Report

A Rare Presentation of Pseudotumor Cerebri Secondary to Growth Hormone Therapy in a Child with Panhypopituitarism

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ABSTRACT

Pseudotumor cerebri is an increase in intracranial pressure with no evidence of an intracranial space-occupying lesion. It is considered a rare complication of growth hormone therapy. We report a rare case of a 7-year-old boy with panhypopituitarism presenting with pseudotumor cerebri after three months of growth hormone replacement therapy. Intracranial pressure normalized after withdrawal of growth hormone therapy, addition of acetazolamide, and serial therapeutic lumber punctures.

KEYWORDS: Pseudotumor cerebri, growth hormone therapy, panhypopituitarism.

INTRODUCTION

Between 1958 and 1985, growth hormone (GH) was used only to treat children with severe GH deficiency. These GH preparations were relatively crude products extracted and purified from cadaveric human pituitaries. In 1985, Creuzfeldt-Jakob disease was discovered in recipients of GH, and for that reason, use of extracted pituitary human GH was stopped. In the same year, recombinant GH became available [1].

The US Food and Drug Administration approved growth hormone therapy for the following growth disorders: GH deficiency, Turner syndrome, chronic renal failure, children born small for gestational age, Prader-Willi syndrome, and juvenile chronic arthritis. People with these disorders receive recombinant human GH (rhGH) therapy [2].

The overall safety profile of rhGH is considered to be favorable, but it is important that the patient be monitored during therapy because of increased risks of certain side effects. Examples are hyperglycemia with insulin resistance, slipped capital femoral epiphysis, scoliosis, increased growth of nevi, and pseudotumor cerebri, the earliest possible side effect. The incidence of pseudotumorcerebri in patients newly started on GH therapy ranges between 0.1% and 0.2%. Although it's a rare condition in children, it is well known that rhGH-induced pseudotumor cerebri is dose-dependent and occurs mostly within the first months of therapy [3–7].

Pseudotumor cerebri is a condition where intracranial pressure is elevated to more than 24 cm water in the absence of clinical, laboratory, or radiological evidence of an intracranial space-occupying lesion with normal cerebrospinal fluid (CSF) components. The classical symptoms are headache, nausea, and vomiting. Patients may also complain of neck stiffness, blurred vision, and double vision with normal levels of consciousness [6,8,9].

We report a rare case of pseudotumorcerebrias a complication of GH therapy in a 7-year-old Saudi boy with panhypopitueterism.

CASE REPORT

A 7-year-old Saudi boy presented to the Pediatric Endocrine Clinic, King Abdulaziz Hospital with short stature. He was full term, born weighing 3.2 kg with a good Apgar score. He had no history suggesting prenatal birth asphyxia, maxillary natal tooth at delivery, prolonged jaundice, or neonatal hypoglycemia; however, he had a history of micropenis. His parents were worried about his poor growth velocity, which was 2 to 3 cm per year over the prior 2 years despite their efforts to provide him with high-calorie food supplements. Because he was not growing well, they sought medical advice at the endocrine clinic. The patient had no history of chronic disease, and his family history was negative for short stature.

Upon physical examination, we found his height was 108 cm (-3.11 standard deviation [SD]), his weight was 19 kg (-1.83 SD), and his BMI was 16.4 kg/m^2. His upper- to lower-segment ratio was 1:1 (proportionate short stature). A general examination revealed no evidence of dysmorphic features or midline facial defects. Systemic examination was normal apart from a short stretched penile length of 3 cm, which is below third percentile for his age.

He was investigated thoroughly, and no evidence of iron deficiency anemia, malabsorption disease (especially celiac disease), or liver, renal, or electrolyte dysfunction was found. Timed urine and blood osmolality were normal. Bone age was that for a child two years of age (five years less than his chronological age). A series of endocrinological tests measured basal Insulin-like growth factor 1 (IGF-1), Insulin-like growth factor binding protein 3 (IGFBP3), basal and stimulated adrenal axis hormones (ACTH and Cortisol), TSH, fT4, LH, FSH, and Testosterone. In addition, a test for pharmacologically stimulated GH using Clonidine and Glucagon was performed (**Tables 1 and 2**). Results confirmed panhypopitueterism with GH, TSH, ACTH, and Gonadotropin deficiencies. Magnetic resonance imaging of the brain and pituitary revealed an ectopic posterior pituitary gland and empty sellaturcica, which were causing panhypopitueterism (**Figure 1**).

Table 1: Basal hormonal workup

Hormone	Result	Normal range
TSH	1.99	0.27 – 4.2 uIU/L
FT4	8.5	12-22 Pmol/L
LH	0.2	Less than 2
FSH	0.2	Less than 2
Testosterone	0.087	8.4 – 28.7 nmol/L
IGF-1	601	1600 – 6500 ng/ml

Table 2: Stimulated hormonal panels of GH & Adrenal axes.

Time	GH Levels (any value above 10 ng/ml)	ACTH Levels (1.6-13.9 Pmol/L)	Cortisol Levels (138 -636 nmol/L)
30 minutes	0.100	3.74	51.07
60 minutes	0.255	3.86	51.71
90 minutes	0.271	3.50	41.48
120 minutes	0.276	4.06	65.24
150 minutes	0.344	3.71	52.26
180 minutes	0.285	3.27	72.97
210 minutes	0.186	1.60	

The patient was started on hormone replacement therapies including therapeutic daily doses of growth hormone at 30 micrograms/kg, hydrocortisone at 10 mg/m^2, thyroxin at 25 micrograms, and testosterone injected intramuscularly at 50 mg monthly for three months.

After five weeks, he presented acutely with severe headache, neck pain with rigid flexion, vomiting, diplopia, and squint in the right eye. No fever, rash, change in behavior, or abnormal movements were evident. Examination revealed a temperature of 36.3 C, a heart rate of 120 beats/minute, blood pressure of 105/70 mmHg, a Glasgow Coma Scale score of 15/15, equally reactive pupils, negative Kernig's and Brudziniski's signs, normal power, tone and intact reflexes in both the upper and lower limbs.

Upon an ophthalmological examination, the patient had right-eye squint due to 6th nerve cranial palsy, corrected visual acuity of 20/20 bilaterally, and intraocular pressures of 11 in the right eye and 14 in the left eye. Fundoscopy showed signs of papilledema, bilateral hyperemic optic nerve, and increased retinal vessel tortuosity. He was thoroughly examined to rule out central nervous infections, tumors, and hemorrhage. A CSF tap was performed after brain imaging, and it shown no evidence of meningitis, encephalitis, or brain hemorrhage. The CSF opening pressure was elevated at 30 cm water.

An urgent computed tomography (CT) scan was performed (**Figure 2**), and findings were consistent with pseudotumorcerebri. Also, CT venography showed no evidence of thrombosis. Symptoms were managed by withholding GH therapy. Acetazolamide at 500 mg was given twice daily with serial therapeutic lumbar puncture to relieve increased intracranial pressure and visual deteriorations. The patient's condition improved gradually, with complete recovery within 2 months.

Figure 1: Brain Magnetic Resonance Imaging showing ectopic posterior pituitary gland and empty sellaturcica

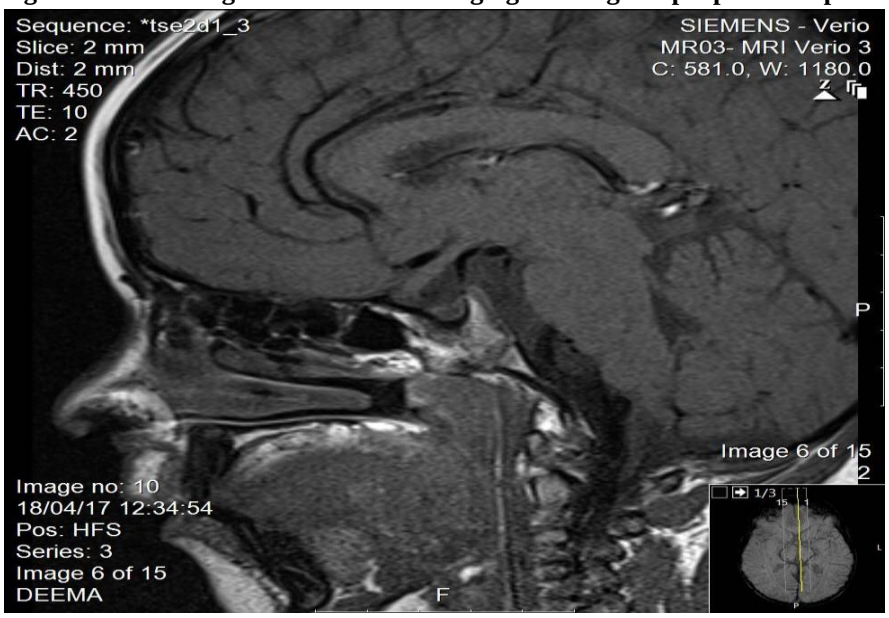
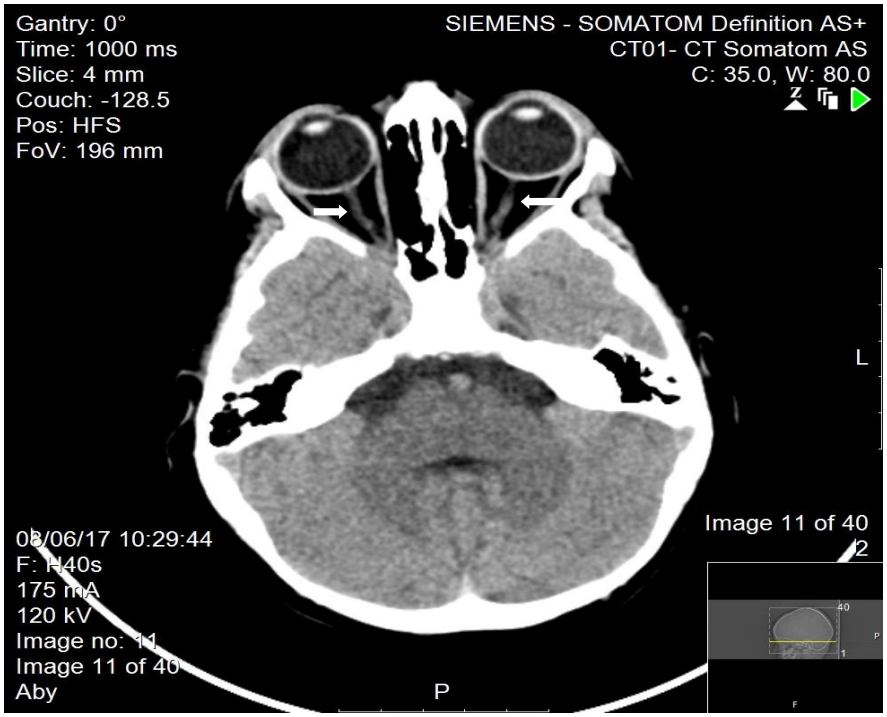


Figure 2: Brain CT Scan showing enlarged and tortuous optic nerve sheathes bilaterally



DISCUSSION

Empty sellaturcica is considered to be a risk factor for developing pseudotumor cerebri[6]. Increased intracranial pressure was documented in 10% of those with untreated empty sella. The theory behind this complication is that an incompetent sellar diaphragm allows herniation of the subarachnoid fluid [10,11]. Children with this condition and GH deficiency may be prone to rhGH-induced pseudotumor cerebri[12]. This index case showed no clinical evidence of pseudotumorcerebriprior to GH therapy.

The pathogenesis of rhGH-induced pseudotumorcerebriis described as direct action of rhGH on the choroid plexus, increasing CSF production secondary to an increase in GH concentrations in the CSF. The renin-angiotensin system might have a role in the pathogenesis of this condition via alterations in sodium and water retention [2,5,12].

The association between rhGH and pseudotumor cerebriwas first reported 25 years ago in two patients [13]. Subsequently, Malazowki et al reported 22 children and an adult treated with recombinant GH or IGF-1 who developed pseudotumorcerebri. In 1995, Malozowski reported 13 children in the United States who developed pseudotumorcerebrisecondary to rhGH therapy. Koller identified 15 cases of pseudotumorcerebriout of 1670 children on rhGH therapy to treat short stature secondary to

chronic renal failure. The number reportedly increased as rhGH use became more frequent over longer periods and at higher doses. Various other reports confirm the association between rhGH and pseudotumor cerebri[9,10,14].

It is well known that pseudotumorcerebrisecondary to rhGH therapy is dose dependent. In a majority of reported cases, symptoms of pseudotumorcerebrideveloped at dosages between 0.17 and 0.35 mg/kg/day. It occurs at any time, but has been seen as early as one week and as late as 5 years after beginning therapy [10,12]. In this index case, the patient was started on rhGH at 30 micrograms/kg/day. Symptoms of pseudotumorcerebristarted one month after initiation of therapy.

Pseudotumor cerebri could resolve spontaneously, but treatment is indicated if headaches persist or if visual involvement occurs. The standard treatment for pseudotumor cerebriis a temporary withholding of GH therapy and use of diuretics, most notably acetazolamide [5]. Further management, including serial lumbar punctures, surgical procedures such as the CSF diversion procedure, and optic nerve fenestration are recommended if response to acetazolamide is inadequate or if visual deterioration occurs, as in this case [5]. In the majority of cases, complete resolution occurs within weeks or as late as 3 to 6 months later [2,5,12,15–17]. Restarting GH at a similar dose could cause recurrence of pseudotumor cerebri; several studies show that restarting GH therapy in smaller doses could prevent recurrence [2,5].

CONCLUSION

Although pseudotumorcerebriis a rare complication of GH therapy, it should be suspected in any child presenting with headache or clinical features of increased intracranial pressure. Pediatricians and endocrinologists should have a high index of suspicion for this rare complication.

Conflicts of interest: There are no conflicts of interest

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