

Case Report

Prolonged Intracranial Hypertension after Recombinant Growth Hormone Therapy due to Impaired CSF Absorption

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Abstract. We experienced a case of a Japanese boy who developed intractable idiopathic intracranial hypertension (IIH) during growth hormone (GH) treatment. At the age of 4 yr, the boy was diagnosed with idiopathic growth hormone deficiency, and recombinant human GH replacement was initiated. Nine months after initiation of the GH therapy, he began to complain of headache, but papilledema was not observed. His headache persisted thereafter, and right esotropia occurred 10 mo after the initiation of GH therapy, at which time papilledema was detected. No other neurological abnormalities were detected, and the findings of computed tomography and magnetic resonance imaging were normal. In a cerebrospinal fluid (CSF) examination, the pressure was markedly elevated to 450 mmH₂O, but no other abnormality was recognized. Impaired CSF absorption was detected using the pressure-volume index technique. The CSF levels of GH and insulin-like growth factor I were not increased. GH therapy was withdrawn after it was suggested that the IIH was associated with the GH therapy, but the headache persisted. The intracranial hypertension did not respond to diuretics, and prednisolone was only transiently effective. Although the fundoscopic findings were normalized, increased CSF pressure was still observed. For over 2 yr, repeated lumbar puncture was necessary to protect against visual defect. IIH is an uncommon adverse event during GH therapy, but it must be considered carefully.

Key words: intracranial hypertension, growth hormone, insulin-like growth hormone, CSF absorption

Introduction

Idiopathic intracranial hypertension (IIH), also known as pseudotumor cerebri, is a condition

of increased intracranial pressure without clinical, laboratory or radiological evidence of intracranial pathology. IIH has been related to the use of many medications, such as tetracycline, vitamin A and thyroid hormone, but it rarely occurs in childhood. Since the first report of IIH during growth hormone (GH) therapy in 1992 (1), cases have been reported abroad (2, 3), but there have been no documented cases of IIH during GH therapy in Japan (4). The

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pathophysiology of IIH is still not fully understood. It usually resolves after a few months, but the risk of visual deterioration is considerable, and some patients experience a chronic disabling course for many years (5).

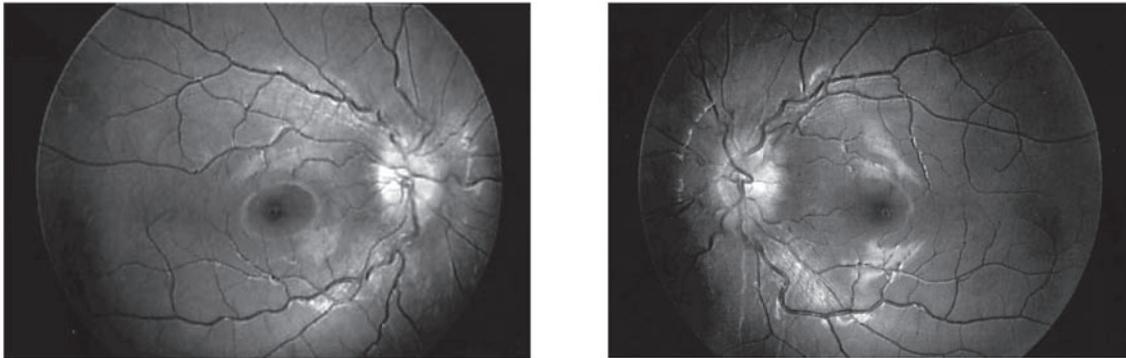
Case Report

A 4-yr-old Japanese boy was referred to our department because of headache and esotropia. His height was 89.7 cm (-3.1 SD for Japanese boy standard), and he weighed 10.8 kg. He was born at 39 wk of gestation by normal delivery, weighing 2,624 g. His growth rate was poor from 1 yr of age. Since his height was -3.0 SD, he was examined at 2 yr of age. The peak GH values with insulin tolerance and clonidine loading were 7.1 and 8.4 ng/ml, respectively. His serum GH concentration was measured with an immunoradiometric assay kit using recombinant GH as the standard. The response to cortisol was normal, as was the TRH-induced responses of TSH and prolactin. The concentrations of insulin-like growth factor I (IGF-I), free T_4 and TSH were 22 ng/ml, 1.2 ng/dl and 2.2 μ U/ml, respectively. From these results, partial idiopathic growth hormone deficiency (GHD) was diagnosed according to the 2003 revised version of the criteria for GHD of the Ministry of Health, Labour and Welfare. Recombinant human GH replacement (0.175 mg/kg/wk) was started at the age of 3 yr. Nine months after initiation of GH therapy, he began to complain of headache, but papilledema was not observed. His headache persisted thereafter, and right esotropia due to right abducens palsy occurred 10 mo after initiation of GH therapy, at which time bilateral papilledema was detected (Fig. 1). No other neurological abnormalities were detected, and his computed tomography (CT) scan, magnetic resonance (MR) imaging and EEG findings were normal. No abnormalities were detected on routine examination, and his IGF-I concentration was 103 ng/ml. In a cerebrospinal fluid (CSF) examination (Table 1), the opening pressure was

markedly elevated to 450 mmH₂O, but the cell count (13/mm³), protein concentration (26 mg/dl) and glucose concentration (85 mg/dl) were normal, and culture was negative. The CSF levels of GH, IGF-I, myelin basic protein (MBP) and neuron-specific enolase (NSE) were not elevated (6, 7). To evaluate the mechanism of the IIH, CSF formation and absorption were measured using the pressure-volume index (PVI) technique (8) 10 and 13 wk after the onset of IIH. The results showed that CSF formation was normal but that the absorption was significantly impaired (Table 2).

GH therapy was withdrawn after it was suggested that the IIH was associated with the GH therapy. However, the headache was refractory and did not respond to 10 mg/d of furosemide, 100 mg/d of acetazolamide or 200 ml/d of glycerol. With the initiation of 10 mg/d of prednisolone concomitantly, the CSF pressure fell to 150 mmH₂O, and the headache improved. Thereafter, the prednisolone was tapered over 2 wk and discontinued. However, since the headache reappeared 10 d after withdrawal of prednisolone, lumbar puncture was performed, which revealed elevation of the CSF pressure to 250 mmH₂O, while the cell counts and protein concentration remained normal. At 3 mo after withdrawal of GH replacement, his fundoscopic findings normalized (Fig. 1). However, his headache was uncontrollable with furosemide and acetazolamide administration, and therefore recurrent lumbar puncture was required to control the symptoms. At 21 wk after onset, the abducens palsy transiently appeared again, but papilledema was not observed. Repeated MR images depicted no abnormal findings of hydrocephalus, tumor or multiple sclerosis. Increased CSF pressures (greater than 250 mmH₂O) were observed intermittently for about 2 yr; lumbar puncture was performed repeatedly to protect his visual acuity. Since then, the intracranial hypertension and abducens palsy has ceased to be detected. His growth velocity has decreased, but the GH therapy has not been resumed.

10 mo after GH therapy



12 wk after the onset of IIH

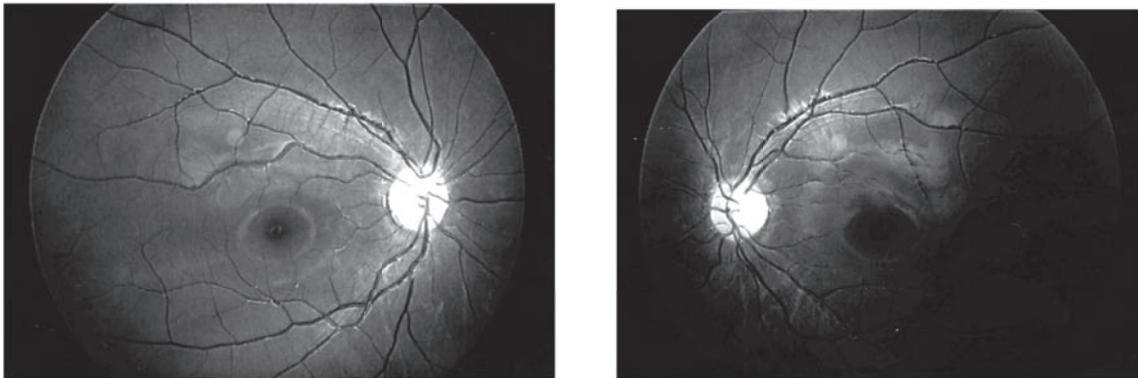


Fig. 1 Fundoscopic findings: remarkable papilledema in both eyes at 10 mo after GH therapy (upper). Papilledema was improved at 3 mo after withdrawal of GH replacement.

Table 1 Summary of laboratory data (CSF)

Weeks of illness	8*	11	13	23
Initial pressure (mmH ₂ O)	450	260	130	150
Cell counts (/mm ³)	13	0	2	1
Protein (mg/dl)	26	13	13	14
GH CSF (ng/ml)	0.03	0.03	0.04	0.03
IGF-I Serum (ng/ml)	103			80.3
CSF (ng/ml)	< 10	< 10	< 10	< 10
MBP [<102 pg/ml]	< 31.2	< 31.2	< 31.2	< 31.2
NSE [4–8 ng/ml]	1.4	3.0	2.2	3.4

*On admission. Age-matched reference levels in CSF: GH 0.026 ± 0.028 ng/ml (6) and IGF-I 6.9 ± 0.6 ng/ml (7). MBP: myelin basic protein. NSE: neuron-specific enolase. Reference levels are indicated in square brackets.

Table 2 Data for pressure-volume index (PVI), CSF formation and outflow resistance

Weeks of illness	10	12
PVI by withdrawal (ml)	8.31	28.70
CSF formation rate [0.36 ± 0.58 ml/min]	0.12	0.68
PVI by injection (ml)	17.86	14.03
Resistance to CSF absorption [2.9 ± 0.8 mmHg/ml/min]	45.13	82.46

The reference levels according to Shapiro K *et al.* (Annal Neurol 7, 1980) are indicated in square brackets.

Discussion

IIH is a condition in which the CSF pressure is elevated despite the absence of an intracranial space-occupying lesion or hydrocephalus. It is characterized by increased CSF pressure with normal CSF composition, headaches, vomiting, papilledema and strabismus. Permanent visual defects are a serious complication of IIH. In the present case, persistent headache, right abducens palsy and bilateral papilledema without other neurological abnormalities were recognized, and MR imaging and EEG findings were normal. A CSF study showed marked intracranial hypertension but a normal cell count and protein concentration, and culture was negative. The CSF levels of MBP and NSE were not elevated. Acute disseminated encephalomyelitis, multiple sclerosis and tumors were unlikely based on the clinical course and serial MR imaging. These findings were compatible with IIH.

IIH is one of the well-known adverse effects related to GH therapy. In the Kabi International Growth Hormone Study (KIGS) of 2007 (3), the incidence of IIH as an adverse event during rhGH replacement for idiopathic GHD was 13/100,000 treatment years, and IIH developed 2 wk to 8 yr after initiating GH therapy at a dose of 1.08–0.33 mg/kg/wk (3). The risks of IIH differ between diagnostic groups, with the highest incidence in children with chronic renal failure, 130/100,000 treatment years, and a higher incidence observed with Prader-Willi (79/100,000) and Turner

(58/100,000) syndromes (3). Other national surveillance studies also suggest that GH treatment increases the risk of IIH (9, 10). There are no sex-related differences in children with IIH, but obesity is a risk factor for IIH (11). Although no documented cases of IIH with GH therapy have been reported in Japan (4), in which rhGH is used widely, it is possible that undiagnosed IIH is more common than one might expect. Headache at the start of GH therapy is the most common side effect listed in the KIGS database and is usually transient (3). However, the incidence of headache as an adverse event of GH therapy in Japan is less frequent than that in the global study (4). It is likely that headache is underreported and that some cases of mild IIH resolve spontaneously.

Although the pathogenesis of IIH is uncertain, it is thought to involve increased production of CSF (12, 13) and/or compromised CSF absorption (14–16). It has been suggested that rhGH passes through the blood-brain barrier and induces increased levels of GH in the CSF (17). The direct action of rhGH at the choroid plexus, thus, augments IGF-I and in turn CSF production (18). In our patient, the levels of GH and IGF-I were not increased, but CSF absorption was impaired rather than CSF formation as measured by the PVI technique. The CSF absorption disturbance in our case was related to the rhGH replacement therapy, but the definitive mechanism was obscure.

The prognosis of IIH is generally favorable,

but it sometimes results in severe visual impairment. If withdrawal of GH therapy does not improve the symptoms, diuretics and steroids are administered. If these drugs are not effective, repeated lumbar puncture, lumboperitoneal or ventriculoperitoneal shunts are necessary (19). In our patient, the IIH symptoms occurred 9 mo after initiation of GH therapy, the refractory headache did not respond to furosemide, acetazolamide or osmotic diuretic and prednisolone was only transiently effective. Although the fundoscopic findings and abducens palsy were normalized, an increased CSF pressure was still observed. For over 2 yr, repeated lumbar puncture was necessary to control the IIH. Losses of visual acuity or visual fields are serious permanent complications of IIH, and management strategies are designed to avoid these problems. Surgical intervention is only required when there is a risk of visual loss.

When headache occurs early in the course of GH therapy, it is necessary to exclude IIH by funduscopy. In patients with IIH, other indefinite complaints, such as dizziness, back or neck pain, mood change and irritability, may also be present. IIH is an uncommon adverse event during GH therapy, but it must be considered carefully.

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