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Two Cases of Generalized Seizures During Growth Hormone Therapy

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We report two patients experienced generalized seizures during growth hormone (GH) therapy. One patient suffered from febrile seizures, epilepsy and idiopathic short stature and other patient suffered from Noonan syndrome and GH deficiency (GHD). It is difficult to make an association between GH therapy and increased incidence of seizures, because our two cases has the potential to induce seizures. Also, we have experienced 7 cases that suffered from epilepsy and GHD and no change with regard to the incidence, duration or type of seizures during GH therapy. These results may indicate that the potential of GH to induce seizures is very low.

Key words: growth hormone deficiency, growth hormone therapy, Noonan syndrome, adverse events, epilepsy

Introduction

Growth hormone (GH) consists of 191 amino acids and is produced in the anterior pituitary. It possesses a variety of biological activities in addition to its ability to stimulate the growth of skeletal and soft tissues[1]. In particular, there have been increasing numbers of reports on the effect of GH on the central nervous system (CNS). These reports suggest that GH can pass through the blood-brain barrier to bind to GH receptors in the choroid plexus, hypothalamus, hippocampus and cortex, indicating that GH may be involved in development of cognitive function, memory, motivation and behavior[2)3)].

Reported adverse events during GH therapy include brain tumors recurrence, impaired glucose tolerance, scoliosis and seizures. In annual reports from the Kabi Pharmacia International Growth Study (KIGS), the incidence of seizures as an adverse event of GH therapy was reported to be 0.6%[4].

Case Reports

Case 1

A boy, now aged 11 years, was born very premature (25 weeks gestation) in a breech position, with a low birth weight (831 g) and height (33.5 cm). He was immediately intubated and given oxygen therapy for asphyxia. He was also given phototherapy and treatment with surfactant. By the age of 6 years and 1 month, his height and bone age were 96.3 cm (−3.7 standard deviation (SD)) and 3 years and 1 month, respectively. He was given an insulin loading test, L-dopa loading test and a spontaneous GH secretion profile at night. The peak concentration of GH was 25.5 ng/ml under insulin loading and 8.1 ng/ml under L-dopa loading. The average level of GH secretion during sleep was 0.84 ng/ml. The concentration of IGF-1 was 125 ng/ml. He was diagnosed with idiopathic short stature, but commenced GH therapy (0.175 mg/kg/week) at the age of 6 years and 4 months, because of poor GH secretion during sleep (Fig. 1A).

At the age of 1 year he experienced four febrile seizures and moderate mental retardation (4 years, 6 months: IQ=53, 11 years, 5 months: IQ=48). He experienced further febrile seizures at the ages of 6 years and 6 months, and 7 years and 11 months. At the ages of 9 years and 11 months, 10 years and 2 months, and 10 years and 3 months, he suffered from generalized tonic seizures without fever, each lasting for about 1 minute. An electroencephalogram (EEG) performed at the age of 6 years and 6 months showed a pseudo petitmal discharge during

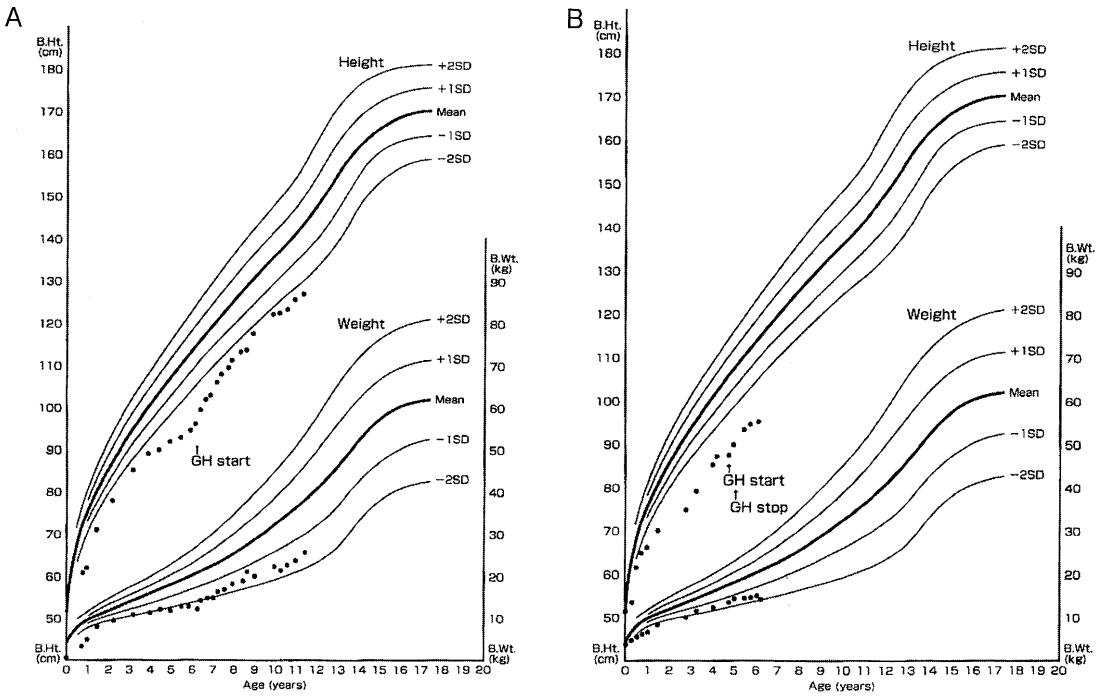

Fig. 1 Cross-sectional growth chart for boy (0-18 years)
A: Case 1. B: Case 2.

sleep, but no further abnormalities were detected. Blood sugar levels, biochemistry, brain computed tomography (CT) and magnetic resonance imaging (MRI) examination, were all normal. He had never received anticonvulsant medication. He is currently receiving GH treatment.

Case 2

A boy, now aged 6 years, was born at 36 weeks gestation with a birth weight of 3,730 g and a height of 51 cm. He subsequently underwent phototherapy for hyperbilirubinemia. He was hypotonic and found to have a ventricular septal defect. His developmental quotient (DQ) at the age of 2 years and 4 months was 54, and he was karyotyped as 46XY. He was diagnosed as having Noonan syndrome on the basis of features including hypertelorism, epicanthus, exophthalmos, nystagmus, low set ears, saddle nose, webbed neck, hypotonia, short neck, short limbs, cubitus valgus, and a large head. At the age of 4 years and 4 months, his height and bone age were 87.0 cm (−3.6 SD) and 2 years and 6 months, respectively. He was given an L-dopa loading test and an arginine loading test. The peak concentration of GH was 3.6 ng/ml under L-dopa loading and 6.9 ng/ml under arginine loading. The average level of GH secretion during sleep was 3.0 ng/ml, while that of IGF-1 was 56 ng/ml. He was diagnosed with GH deficiency (GHD) and GH therapy (0.175 mg/kg/week) was started at the age of 4 years and 10 months (Fig. 1B).

At the age of 5 years and 1 month, he contracted influenza and developed febrile status epilepticus (generalized tonic seizures, dominant on the right side, that persisted for 60 minutes). After recovery from the seizures, a right hemiplegia persisted for some time. During this time no seizures were experienced. GH was withdrawn and 2 months later he again suffered from status epilepticus (body temperature 37.5℃, the generalized tonic seizures lasted for 40 minutes.) At that time, an EEG showed a diffuse spike and wave complex mixed with slow waves in the right hemisphere (Fig. 2). Mild atrophy was detected after the first episode of status epilepticus on a brain CT and severe atrophy was demonstrated with a brain MRI following the second episode (Fig. 3). Despite the use of anti-convulsant medication following the second episode, seizures continued with a frequency of 5-10/day. Tests per-

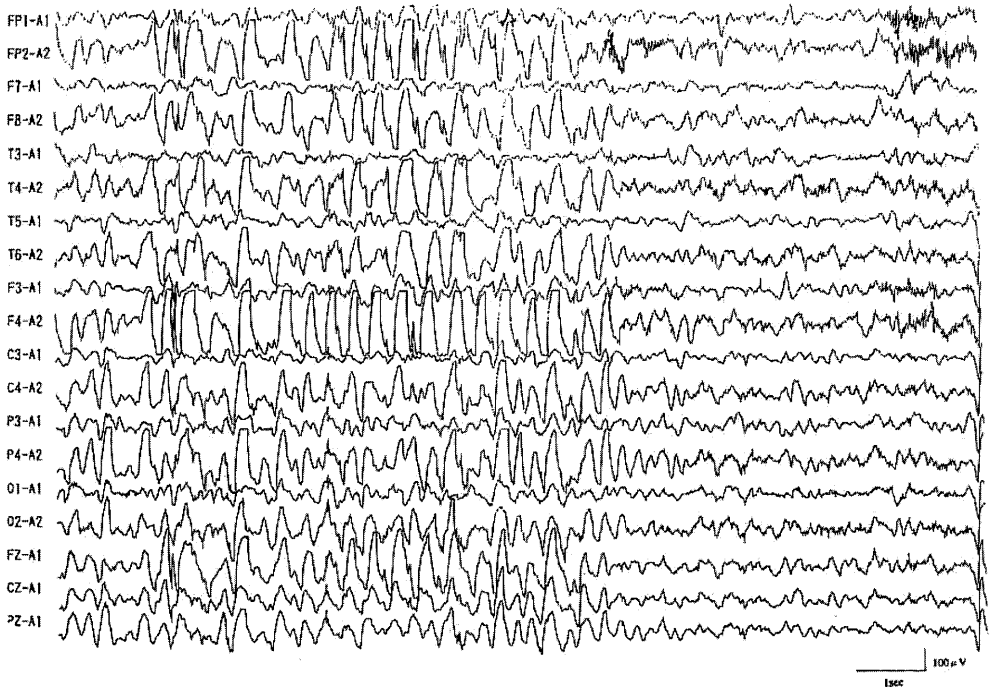

Fig. 2 EEG (electroencephalogram)
Diffuse spike and wave complex mixed with slow waves in right hemisphere in Case 2.

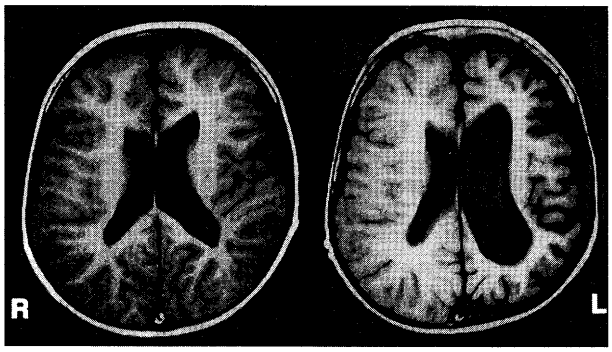

Fig. 3 MRI
Left: Mild brain atrophy at 5 years 1 month in Case 2.
Right: Severe brain atrophy at 6 years in Case 2.

formed following the episodes of status epilepticus failed to detect any abnormalities in blood or urine. Similarly, the results of amino acid tests and investigations into the metabolism of organic acids were also normal.

Discussion

One of the two reported cases describes a patient with febrile seizures and epilepsy and the other describes a patient with Noonan syndrome. Within the general population, the incidence of febrile seizures is 2-5% and the transition rate to epilepsy is 2-7%[5)6)]. A patient with febrile seizures, epilepsy and moderate mental retardation was reported (case 1). The seizures disappeared spontaneously, although the patient was receiving GH. In addition to the cases presented here, we investigated 7 other patients with epilepsy that underwent GH treatment (Table). The condition of none of these patients worsened during the course of treatment with regard to the incidence, duration or type of epileptic seizures. This may indicate that the potential of GH to induce seizures is very low.

Noonan syndrome has features including short stature, abnormal gonads and cardiac anomalies. It may also be complicated by disturbances in the CNS and the incidence of epilepsy in patients with Noonan syndrome is approximately 10%[7)]. The transition rate from febrile status epilepticus to epilepsy is in the range of 6-7% and is significantly higher than that from simple febrile seizures to epilepsy[8)9)]. For case 2, high fever was thought to induce status epilepticus accompanied by both hemiconvulsion and hemiplegia, and may fit the so-called hemiconvulsion, hemiplegia and epilepsy syndrome

Table The relationship between seizures and GH therapy

Case	Age	Sex	Seizure type	Onset of seizures	EEG	Anticonvulsant therapy	Start age of GH therapy	GHD
1	11Y	M	GTS	1Y3M	abnormal	(−)	6Y4M	I
2	6Y	M	GTS	5Y1M	abnormal	(+)	4Y10M	P
3	10Y	F	GTCS	0Y4M	borderline	(+)	8Y8M	P
4	15Y	F	CPS	0Y7M	abnormal	(+)	10Y4M	P
5	23Y	F	CPS	1Y6M	abnormal	(+)	12Y1M	P
6	15Y	M	GTS	2Y3M	abnormal	(+)	8Y10M	P
7	22Y	M	CPS → GTCS	2Y8M	abnormal	(+)	8Y11M	P
8	11Y	M	SPS	4Y0M	abnormal	(+)	8Y10M	P
9	17Y	F	GTS	9Y3M	abnormal	(+)	10Y11M	P

GTS: generalized tonic seizure, GTCS: generalized tonic clonic seizure, CPS: complex partial seizure, SPS: simple partial seizure, EEG: electroencephalogram, GHD: growth hormone deficiency, I: idiopathic short stature, P: partial GHD.

(HHE syndrome)[10]. In HHE syndrome, brain CT showed hemiatrophy on the contralateral and ipisilateral side that appeared epileptiform discharge on EEG, so contralateral epileptiform EEG abnormality was observed in the patient with severe hemispheric brain damage[11]. As to the EEG abnormality in the HHE syndrome, electrical low voltage and/or slow activity in the damaged hemisphere and epileptiform discharge has been reported. Sometimes epileptiform discharge dominantly appeared on the contralateral side of the damaged hemisphere[12]. In the present case, marked hemiatrophy on brain MRI showed contralateral epileptiform discharge on EEG. In this case, however, the relationship between the administration of GH and seizures is unclear.

According to a report in the adverse events of KIGS, out of 31,462 cases that underwent GH therapy, 174 cases suffered from seizures (0.6%). In 27 cases, epilepsy had been reported before the start of GH treatment. Onset of epilepsy during GH treatment may have occurred in 147 cases (0.5%)[4]. This incidence is not higher than that seen for epilepsy within the general population[12].

The effect of GH on the central nervous system is not fully understood. There have been some reports that treatment of GHD patients with GH results in significant changes in cerebrospinal fluid (CSF) concentration of GH, monoamine, IGF-1, β-endorphin and aspartate[2)13)14)]. While, GH treatment of GH-deficient dwarf rat or aging rat showed the change in GH, GH-releasing hormone, IGF-1 and somatostatin gene expression[15)16)]. At the same time, there is a possibility that these substances are acting as neurotransmitters in the central nervous system. Some reports showed that β-endorphin may have a role in the development of seizures[17]. Meanwhile, plenty of GH receptors sites in the pituitary and hypothalamus may play a role in the regulation for the hormone secretion[18]; additionally they are well distributed in regions of the hippocampus that are known to be important epileptogenic areas.

These facts raise the possibility that the administration of GH may have some effect on the development of seizures. But, it is difficult to make an association between GH therapy and increased incidence of seizures. Because, our two cases had the potential to induced seizures and in 7 patients that suffered from epilepsy and GHD, the frequency of seizures during GH therapy did not change. It is to be further elucidated of GH effect on the seizures.

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成長ホルモン治療中に全般けいれん発作を呈した２症例

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我々は成長ホルモン治療中に全般けいれん発作を呈した２症例を報告する．１例はヌーナン症候群で成長ホルモン分泌不全性低身長症を有している患児で，もう１例は熱性けいれん，てんかんと非内分泌性低身長症の患児である．成長ホルモン治療とけいれん発現頻度の増加に相関を見出すことは困難である．なぜなら我々の２症例はけいれんを誘発させる要因を有している．さらに，我々はてんかん患児で，かつ成長ホルモン分泌不全性低身長症の７例を経験した．成長ホルモン治療中にけいれんの頻度，持続時間，型には変化がみられなかった．これらの結果は成長ホルモン治療がけいれんを誘発させる要因になる可能性は少ないと思われる．