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Case Report

Chiari type 1 malformation associated with central sleep apnea after high dose growth hormone (GH) therapy in a 12-year-old boy: A case report

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Abstract. We describe the case of a short-statured 12-yr-old boy who developed a Chiari type 1 malformation associated with central sleep apnea after administration of high-dose GH therapy, which he had been receiving since the age of 10 yr and 4 mo. He responded well to GH therapy, and his height increased by 18.8 cm in 2 yr. At 12 yr and 4 mo of age, his mother reported that he had developed sleep apnea during the previous year and it had worsened over a month prior to presentation at our hospital. Otolaryngological examination did not reveal tonsillar or adenoidal hypertrophy. Polysomnography demonstrated severe central sleep apnea with an apnea-hypopnea index of 46.5/h. Sagittal T1-weighted magnetic resonance imaging (MRI) demonstrated herniation of the cerebellar tonsils 15 mm below the foramen magnum into the cervical spinal cord. Continuous positive airway pressure therapy initiated prior to performing neurosurgery was ineffective. Following uncomplicated foramen magnum decompression, his breathing pattern during sleep returned to normal. Sagittal MRI examination should be considered in patients who develop sleep apnea during/following administration of GH therapy.

Key words: Chiari type 1 malformation, GH therapy, central sleep apnea, MRI

Introduction

A Chiari type 1 malformation is a congenital or acquired brainstem abnormality characterized by caudal herniation of cerebellar tonsils through the foramen magnum (1, 2). Usually, Chiari type 1 malformations present in adults with neurological symptoms including headache, neck pain, ataxia, lower cranial nerve palsies, and sensory deficits (1, 2). Sleep disorders, especially sleep apnea (3, 4), as well as cases of sudden death have also been reported in individuals presenting with Chiari type 1 malformation (5). Exacerbation of neurological symptoms has been reported in patients with GH deficiency (GHD) and concomitant Chiari type 1 malformation during administration of GH replacement therapy (6–8). To our knowledge, no

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previous reports have described a Chiari type 1 malformation occurring after administration of GH therapy. We report a short-statured patient who developed a Chiari type 1 malformation associated with central sleep apnea during administration of high-dose GH therapy.

Case Report

We evaluated a 12-yr-old boy whose mother complained of development of sleep apnea in the boy who had been treated with GH administration for his short stature since the age of 10 yr and 4 mo. He was delivered normally after 40 wk and 2 d of gestation, and his birth weight and length were 2,920 g and 50 cm, respectively. He related no history of hypoglycemic episodes during the neonatal period or infancy. He demonstrated delayed growth since early childhood, his height was 89.9 cm [–1.0 standard deviation (SD)] at the age of 3 yr, 107.7 cm (–1.4 SD) at the age of 6 yr, and 127.0 cm (–1.8 SD) at the age of 10 yr and 4 mo (Fig. 1). Based on his growth curve, his height velocity standard deviation score was assessed to be approximately –1.5 between the age of 8 yr and 3 mo, and 9 yr and 9 mo. Height potential prediction based on the mid-parental height of his parents was 164.5 cm. High-dose GH therapy (0.35 mg/kg/wk) was initiated at the age of 10 yr and 4 mo at the clinic where he was treated prior to presenting to our hospital. Data pertaining to provocation tests indicating a diagnosis of GHD were not available, and the reasoning for the administration of high-dose GH was unclear because the clinic where he had received the treatment earlier was no longer functional. T1-weighted images observed on magnetic resonance imaging (MRI) prior to administration of GH therapy revealed no abnormalities (Fig. 2-a). He responded well to GH therapy, and his stature increased by 18.8 cm in 2 yr. Beginning at age 12, he received GH therapy at our hospital at a dose of 0.26 mg/kg/wk. His mother reported that when he was 12 yr and 4 mo of age, he was observed to have developed

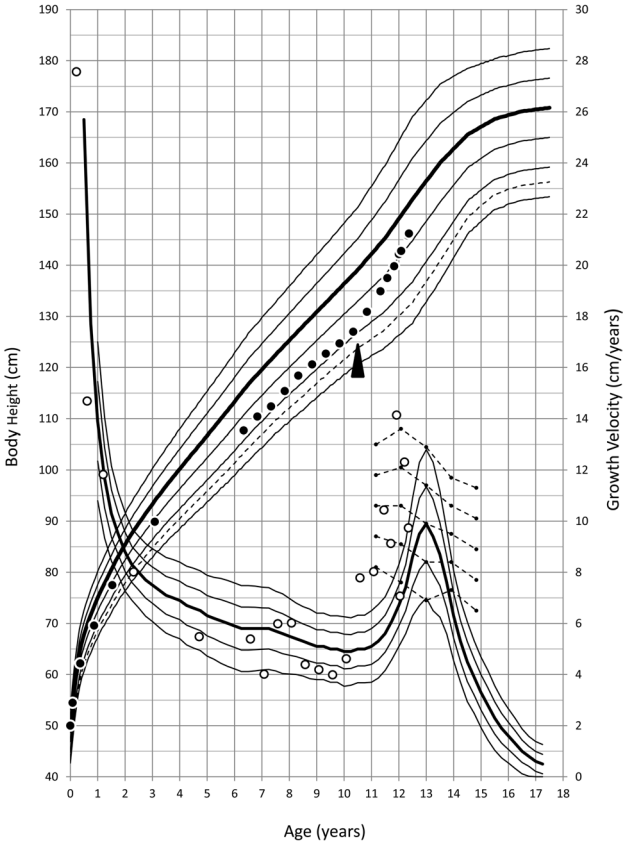

Fig. 1. Longitudinal growth curves and growth velocity in the patient (a 12-yr-old boy). Closed circles indicate height and open circles indicate height velocities. The arrowhead indicates the time when GH therapy was initiated.

sleep apnea during the previous year and this had worsened a month prior to presentation to our hospital.

He was observed to be in a good general condition without any signs of cranial nerve palsies, cerebellar dysfunction, or peripheral motor or sensory nerve deficits. His lower extremity deep tendon reflexes were slightly exaggerated, but the Babinski reflex was bilaterally negative. The remainder of his neurological examination was normal. He was 146.2 cm tall (–0.7 SD) and weighed 39 kg (–0.5 SD). Tanner scale showed genitalia 3, pubic hair 3, and testicular volume > 10 mL. His bone age was 12.6 yr (based on the Tanner-Whitehouse

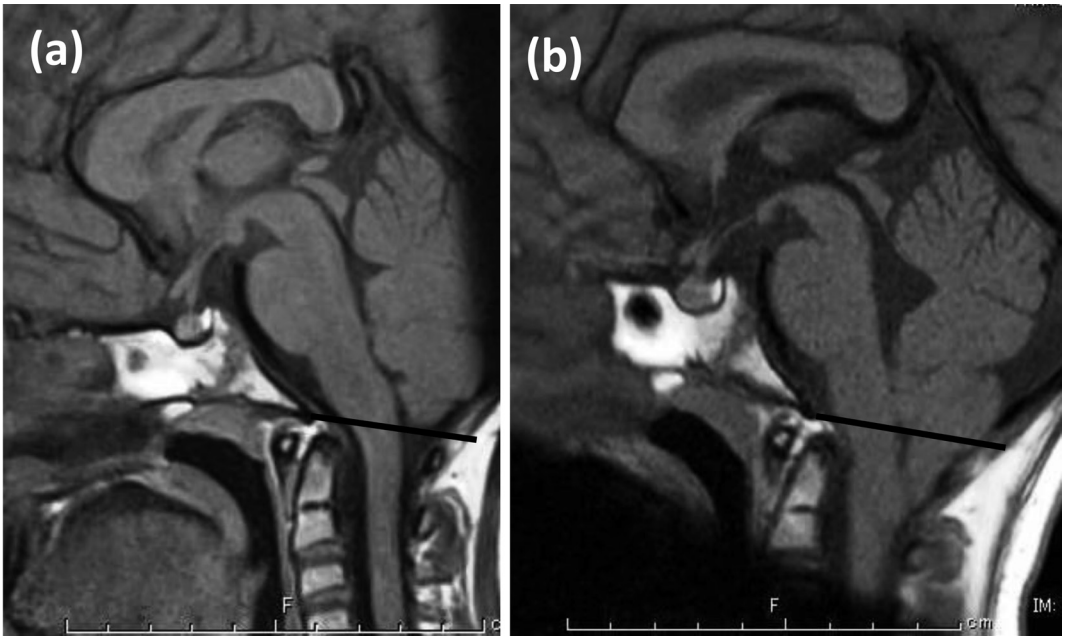

Fig. 2. (a) Sagittal T1-weighted magnetic resonance imaging (MRI) prior to GH therapy showing no abnormalities. (b) Sagittal T1-weighted MRI after GH therapy showing herniation of the cerebellar tonsils 15 mm below the foramen magnum (black line) into the cervical spinal cord.

2 the radius, ulna and short bones method for Japanese individuals). Otolaryngological examination revealed no tonsillar or adenoidal hypertrophy. Laboratory data were generally unremarkable except a serum IGF-1 level of 562 ng/mL, which exceeded the upper limit of the reference range for his age. Polysomnography demonstrated severe central sleep apnea with an apnea-hypopnea index (AHI) of 46.5/h. A sagittal T1-weighted MRI scan demonstrated herniation of the cerebellar tonsils 15 mm into the cervical spinal cord below the foramen magnum (Fig. 2-b, Fig. 3-a). An MRI of the entire spinal cord revealed no abnormalities, including syringomyelia and/or a tethered cord (Fig. 3-b).

We discontinued GH administration after we diagnosed him with having a Chiari type 1 malformation. Continuous positive airway pressure therapy was initiated prior to performing neurosurgery but was observed to be ineffective. We performed posterior cranial decompression with removal of the posterior arch of the C1 vertebra and a duraplasty. He showed no complications and showed a dramatic improvement in his respiratory status during sleep, which was documented clinically and using polysomnography with an AHI 2-4. An MRI obtained 6 months postoperatively demonstrated improvement in the Chiari type 1 malformation (Fig. 4).

Discussion

A Chiari type 1 malformation is characterized by caudal herniation of the cerebellar tonsils through the foramen magnum. The herniated tonsils compress the brainstem and block the normal flow of cerebrospinal fluid. A Chiari type 1 malformation is commonly associated with cervical syringomyelia and typically presents in adults with neurological symptoms, such as headache, neck pain, ataxia, cranial nerve palsies, and sensory deficits (1, 2). Chiari type 1 malformations are diagnosed in adolescents

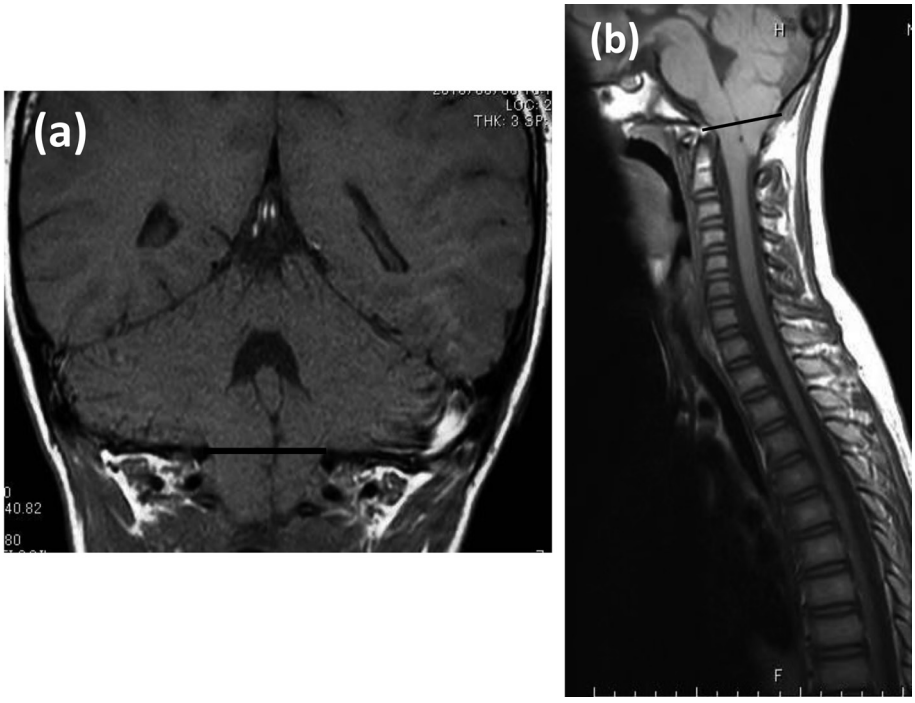

Fig. 3. (a) Coronal T1-weighted magnetic resonance imaging (MRI) prior to surgery showing herniation of the cerebellar tonsils 15 mm below the foramen magnum (black line) into the cervical spinal cord. (b) Sagittal T1-weighted MRI of the entire spinal cord does not show syringomyelia.

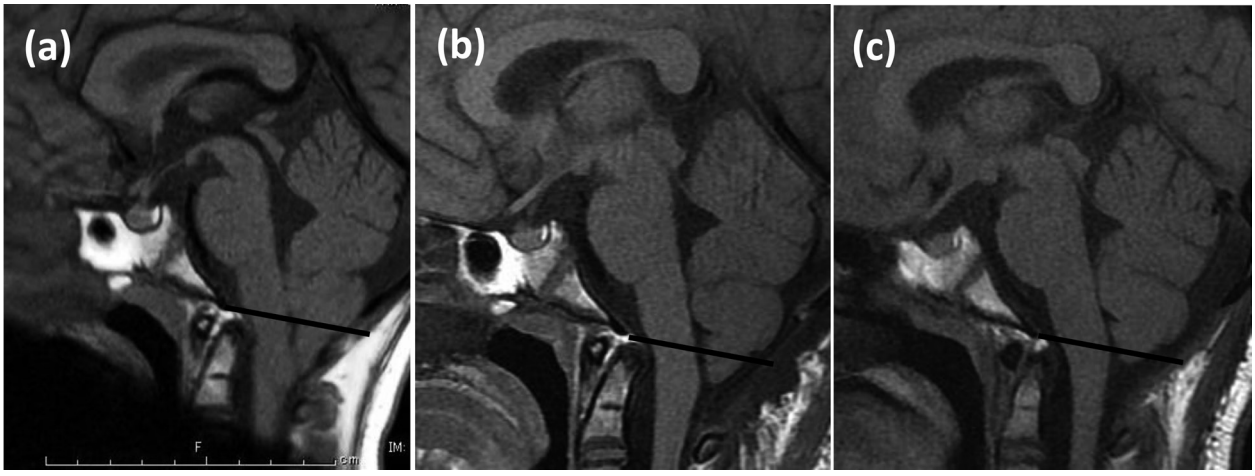

Fig. 4. (a) Sagittal T1-weighted magnetic resonance imaging (MRI) prior to surgery showing herniation of the cerebellar tonsils 15 mm below the foramen magnum (black line) into the cervical spinal cord. (b) Sagittal T1-weighted MRI a week after surgery showing slight improvement in the Chiari type 1 malformation. (c) Sagittal T1- weighted MRI performed 6 mo after surgery showing marked improvement in the Chiari type 1 malformation.

and adults using an MRI in which one or both cerebellar tonsils are observed to be displaced by ≥ 5 mm below the foramen magnum (9). A Chiari type 1 malformation is considered to be a congenital anomaly, although in many cases it is clinically diagnosed only in adults. In extremely rare cases, as was noted in this patient, this malformation may be an acquired anomaly. Usually, acquired Chiari malformations develop secondary to space-occupying lesions such as tumors, arachnoid cysts, and hematomas within the skull, particularly within the posterior fossa (10, 11). An association has been reported between lumboperitoneal shunts used for management of hydrocephalus and acquired Chiari malformations (12).

Hamilton *et al*. (13) have indicated that a Chiari type 1 malformation was observed on MRI examination in 20% of children with isolated GHD, as well as in those showing multiple pituitary hormone deficiencies. Several cases of hypopituitarism associated with Chiari type 1 malformation and syringomyelia have been reported, and in a few of these, it is speculated that GH therapy might have worsened the neurological symptoms of Chiari type 1 malformation (6–8). The pathomechanism explaining the exacerbation of neurological symptoms following GH therapy in patients presenting with Chiari type 1 malformation is considered to be: GH therapy-induced accelerated body growth causes excessive stretching of the spinal cord and compression around the craniocervical junction (8). In contrast, there have been reports that Chiari type 1 malformation disappeared after GH therapy (14).

Regarding the relationship between GH treatment and the onset/development of sleep apnea, Gerard *et al*. (15) have reported that obstructive and/or central sleep apnea may occur in children treated with GH. They described 4 among 145 patients treated with GH who developed sleep apnea (two obstructive, two mixed type). However, this report did not describe the presence of Chiari malformation in these patients. GH therapy is known to produce multiple beneficial effects on growth and body composition, as well as motor and mental development in patients diagnosed with Prader-Willi syndrome (PWS). However, sudden death is known to occur during GH treatment in PWS patients, and 28 deaths have been reported globally among PWS patients who had been receiving GH (16, 17). Common characteristics observed in these patients were that they had been diagnosed with having morbid obesity, and they died of respiratory infections/conditions in the first 9 mo of GH treatment. Therefore, morbid obesity and untreated severe sleep apnea are considered contraindications to GH therapy in patients diagnosed with PWS (16).

In our patient, the Chiari type 1 malformation was not observed on an MRI prior to administration of GH therapy and was detected only 2 yr after administration of GH. To our knowledge, this is the first reported case of a patient with short stature who developed a Chiari type 1 malformation associated with central sleep apnea as the sole neurological complication/sequela/unfavorable manifestation of GH therapy. As a mechanism for the Chiari type 1 malformation onset, we speculated that the cerebellar tonsils were pulled downward by spinal extension due to the sudden height increase with the GH therapy because the cerebellum was binding to the pons with the cerebellar peduncle . Differential growth between bony structures (skull and vertebral column) and the central nervous system might have been responsible for the development of the Chiari type 1 malformation. The development of the Chiari malformation could be attributed to the high-dose GH therapy in our patient because the level of IGF-1 was noted to be higher than the reference range of + 2 SD. However, this dose was the same as the standard dose used to treat short stature born small for gestational age and Turner syndrome. Our patient entered puberty when he was 12 yr 4 mo old. Sex steroids are known to contribute to the accelerated

growth phase associated with puberty. In most instances, a Chiari type 1 malformation remains asymptomatic until adolescence or adulthood, which leads to the speculation that sex steroid-induced growth acceleration might have led to the development of the Chiari type 1 malformation in our patient.

We understand that this patient might not meet the criteria for being categorized as having a GHD based on the guidelines of the Foundation for Growth Science without data pertaining to provocation tests indicating a diagnosis of GHD. We conclude that the Chiari type 1 malformation developed after initiation of GH therapy. Diagnosis of Chiari type 1 malformation is often delayed until symptoms become severe or persistent. Central sleep apnea is a serious risk factor associated with sudden death syndrome. An accurate diagnosis and prompt treatment are important to prevent permanent injury to the nervous system. If this acquired Chiari type I malformation can be reversed by stopping GH therapy, it might be possible to await surgery for a couple of months with the aid of nocturnal respiratory support device, if that is effective. We propose that a Chiari type 1 malformation should be considered in the differential diagnoses of patients presenting with sleep apnea during administration of GH. Furthermore, sagittal MRI examination may be necessary to establish a definitive diagnosis.

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