

Mosaic Turner syndrome with improved Chiari type 1 malformation after growth hormone therapy: A case report

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Abstract. We described a three-year-old girl whose Chiari type 1 malformation associated with mosaic Turner syndrome disappeared after GH therapy. She was diagnosed with mosaic Turner syndrome at the age of 1 yr and 7 mo by a chromosomal analysis (G-band) for short stature and was treated with GH. Sagittal T1-weighted magnetic resonance imaging (MRI) performed before the start of GH demonstrated herniation of the cerebellar tonsils 7 mm below the foramen magnum into the cervical spinal cord. After the initiation of GH therapy, the growth in height was favorable and improved from 70.6 cm (−3.5 SD) to 92 cm (−1.5 SD) in 2 yr. An MRI examination 19 mo later showed the disappearance of Chiari type 1 malformation. GH therapy either exacerbates or ameliorates Chiari type 1 malformations associated with GH deficiency (GHD). Since Turner syndrome uses more GH than GHD, careful follow-up is required if the disease is associated with Chiari type 1 malformation.

Key words: Turner syndrome, Chiari type 1 malformation, GH therapy, resolution, MRI

Turner syndrome, caused by partial or complete loss of an X chromosome, is one of the common chromosomal anomalies in humans. It is typically associated with primary amenorrhea due to early ovarian failure and short stature (1). Abnormalities such as malformations in the central nervous system (CNS) are extremely rare in Turner syndrome, with a few complications of CNS symptoms such as epilepsy and mental retardation. To our knowledge, there was only one report of Turner syndrome with Chiari type I malformation by Harsha KJ *et al.* (2). A Chiari type 1 malformation is a congenital or acquired abnormality of the brainstem, characterized by caudal herniation of cerebellar tonsils through the foramen magnum (3, 4). Exacerbation of neurological symptoms occur in patients with GH deficiency (GHD) and concomitant Chiari type 1 malformation during administration of GH replacement therapy (5–8). GH therapy is also used for Turner syndrome in patients of short stature, at a dose of 0.35 mg/kg/wk, which is twice the dose of GHD.

Previously, we reported a case of Chiari type 1 malformation and severe sleep apnea after high-dose GH therapy, requiring decompression surgery (9). Therefore, at our institution, before the initiation of GH therapy, head MRI checks are conducted for the presence of Chiari

malformation. In this report, we present a case of mosaic Turner syndrome with Chiari type 1 malformation and showed the influence of GH therapy on serial MRI.

Case Report

A girl aged 1 yr and 7 mo was referred to our hospital because of short stature. She was delivered normally after 41 wk and 5 d of gestation, and her birth weight and height were 3070 g and 46 cm, respectively. She demonstrated delayed growth since early childhood. On physical examination, her height was 70.6 cm (−3.5 SD from the mean for normal Japanese girls). There were no physical findings such as a short neck with webbed appearance, low hairline at the back of the head, low-set ears, and a broad chest with widely spaced nipples suggesting Turner syndrome. Her 3-yr-old sister did not have short stature, and her father's and mother's heights were 180 cm and 166 cm, respectively. The height potential prediction based on the mid-parental height was 166.5 cm. Laboratory data were generally unremarkable including serum IGF-1, 36 ng/mL; free T4, 1.45 ng/dL; and TSH, 5.37 IU/L. Her chromosomal analysis (G-band) was conducted after obtaining informed consent. Her karyotype was found to be 45, X

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[19]/47, XXX [11], suggesting mosaic Turner syndrome. Data pertaining to provocation tests were as follows: peak GH levels 19.8 ng/mL to insulin and 18.1 ng/mL to arginine-HCL. Further examination showed no urinary tract or cardiac malformation with normal psychomotor development. T1-weighted images observed on MRI prior to administration of GH therapy, demonstrated herniation of the cerebellar tonsils 7 mm into the cervical spinal cord below the foramen magnum (**Fig. 1**). She was observed to be in good general condition without signs of cranial nerve palsy, cerebellar dysfunction, and peripheral motor or sensory nerve deficits. GH therapy was initiated at the age of 1 yr and 8 mo with informed consent because of the risk of deterioration of Chiari type 1 malformation. The initiation dose was 0.175 mg/kg/wk, which was increased to 0.35 mg/kg/wk 3 mo later. She responded well to GH therapy and her height increased by 9.9 cm in the first 9 mo (**Fig. 2**). There was no significant change in MRI at this point, and spinal MRI showed no evidence of syringomyelia (**Fig. 3a, b**). A year later, her height was 92 cm (-1.5 SD) and an MRI scan showed a marked improvement in Chiari type 1 malformation (**Fig. 4**).

Discussion

Turner syndrome is a rare chromosomal abnormality affecting females. It is characterized by the partial or complete loss (monosomy) of one of the second X chromosomes in some or all cells. Turner syndrome is highly variable among individuals with affected

patients developing a wide variety of symptoms, affecting different organ systems. The common symptoms include short stature and premature ovarian failure making it impossible to reach puberty (1). The clinical phenotype of females with mosaicism for a normal cell line is often milder than that seen in 45,X patients, although this depends on the affected tissues and the timing of development of the mosaicism. In this case, there were no physical findings of Turner syndrome other than short stature. Gross congenital abnormalities of CNS in Turner syndrome are rare, and only a few cases are reported in the literature. To our knowledge, there was only a single report of Turner syndrome with Chiari type 1 malformation by Harsha KJ *et al.* (2).

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 with neurological symptoms in adults, such as headache, neck pain, ataxia, cranial nerve palsies, and sensory deficits (3, 4). Chiari type 1 malformations are diagnosed in adolescents and adults using an MRI where single or both cerebellar tonsils are observed to be displaced by ≥ 5 mm below the foramen magnum (10). The effect of GH therapy on Chiari type 1 malformation

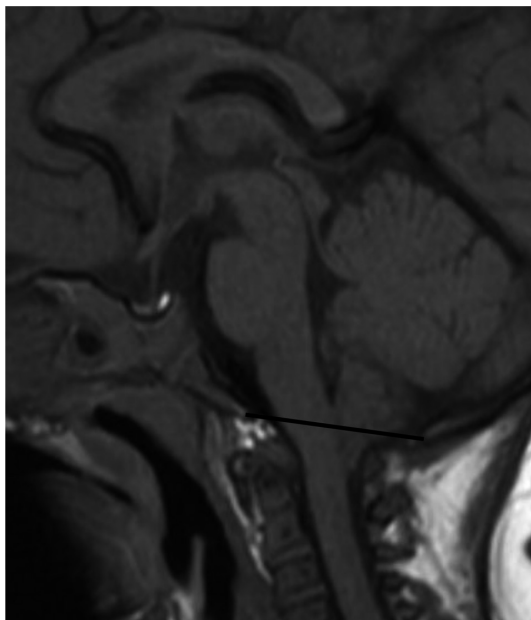


Fig. 1. Sagittal T1-weighted magnetic resonance imaging (MRI) prior to GH therapy showing herniation of the cerebellar tonsils 7 mm below the foramen magnum (black line) into the cervical spinal cord. Posterior fossa appears crowded with effacement of cerebrospinal fluid (CSF) spaces.

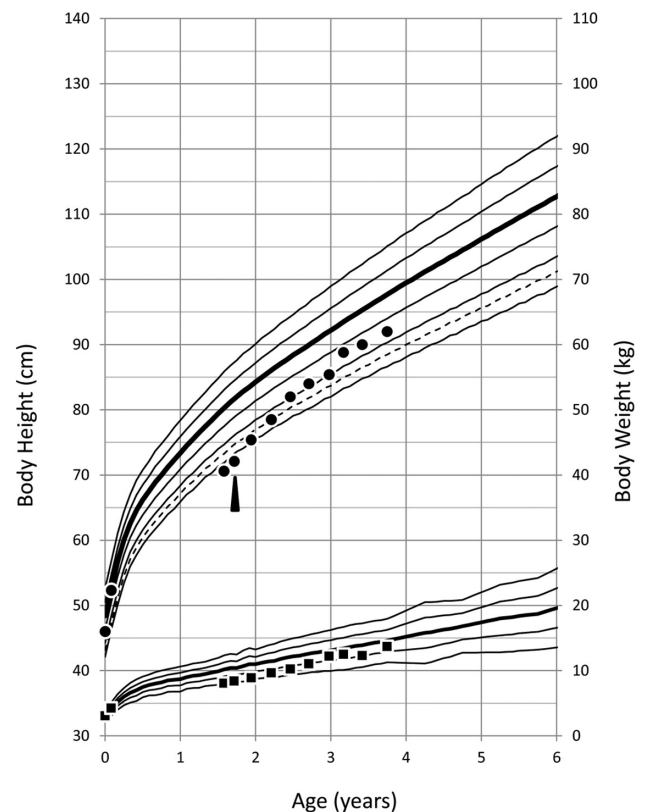


Fig. 2. Growth chart of the patient. Closed circles indicate height and closed squares indicate weight. The arrowhead indicates the time when GH therapy was initiated.

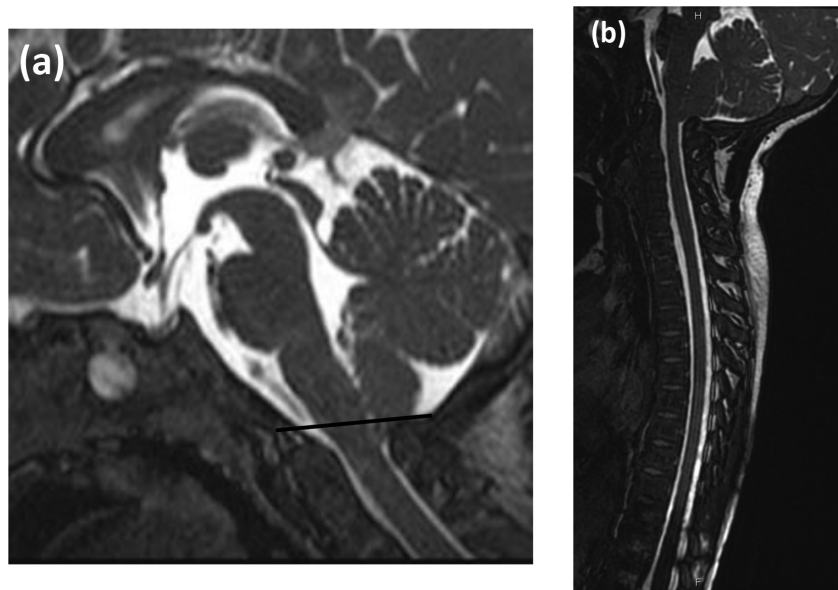


Fig. 3. (a) Sagittal fast imaging employing steady-state acquisition (FIESTA) magnetic resonance imaging (MRI) 9 mo after GH therapy showing no significant changes in the Chiari type 1 malformation. (b) Sagittal FIESTA MRI of the entire spinal cord does not show syringomyelia. The black line indicated the foramen magnum.

associated with GHD is controversial. Some studies have documented clinical decline in patients while on hormone replacement therapy (5–8), whereas others have reported resolution of the radiologic findings after initiating medical therapy (11). Spontaneous resolution of Chiari type 1 malformation in patients without GHD has also been reported (12, 13).

Regarding the incidence of GHD in patients with Chiari type 1 malformation, Ballard H *et al.* (14) recently reported 4.3% of their Chiari malformation patient population (N = 456) with GHD. They described 20 patients with Chiari type 1 malformation and GHD, where 14 patients received GH replacement therapy and six did not. They described that none of the patients with Chiari type 1 malformation and GHD, with or without GH replacement therapy regardless of the change in Chiari type 1 malformation measurement, developed symptoms or syringomyelia, or required surgical intervention (14). Although a subsequent additional report corrected the requirement of decompression surgery in one patient, they concluded, as previously, that the presence of a Chiari type 1 malformation should not prevent initiation of GH therapy (15).

In this case, a Chiari type 1 malformation was found by MRI before the initiation of GH therapy. In our facility, when performing head MRI to detect the cause of short stature before initiation of GH therapy, a sagittal section is taken to check for the presence of a Chiari malformation. In addition to GHD, GH therapy is used for conditions such as Prader-Willi syndrome (PWS), achondroplasia, Noonan's syndrome, and Turner syndrome. Serious adverse events from GH therapy have been reported in PWS. GH therapy is known to produce multiple beneficial effects on growth and body composition, as well as motor and mental development

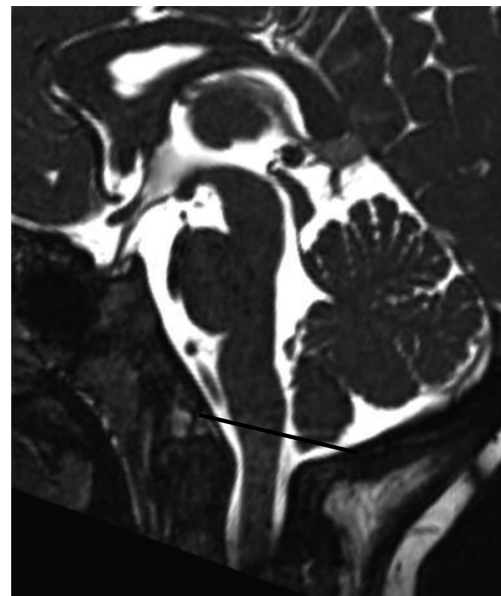


Fig. 4. Sagittal fast imaging employing steady-state acquisition (FIESTA) magnetic resonance imaging (MRI) 19 mo after GH therapy showing marked improvement in the Chiari type 1 malformation. Posterior fossa no longer appears crowded and CFS spaces are visible. The black line indicated the foramen magnum.

in patients diagnosed with PWS. Although Chiari malformations are not clarified, sudden death is known to occur during GH therapy in PWS patients, with 28 such deaths reported globally (16, 17). There have been some reports of Chiari type 1 malformation associated with Noonan's syndrome, a close morphological mimicker of Turner syndrome, without reporting the use

of GH (18). Regarding the mechanism of exacerbation/improvement of Chiari malformation in GH therapy, differential growth between bony structures (skull and vertebral column) and the CNS might have been responsible for the development of the malformation, with spontaneous remission or deterioration depending on the growth balance. There is no conclusive evidence regarding the efficacy of hormone replacement on the Chiari type 1 malformation in children with GHD. Moreover, there is no way to predict which patients will improve versus progress. Although Turner syndrome is seldom associated with Chiari type 1 malformations, if present, careful follow-up is required, as the dose of GH used is 0.35 mg/kg/wk, which is twice the dose of GHD.

Diagnosis of Chiari type 1 malformation is often delayed until symptoms become severe or persistent.

Complications such as central sleep apnea are serious risk factors associated with sudden death syndrome. An accurate diagnosis and prompt treatment prevent permanent injury to the nervous system. Chiari type 1 malformations may be exacerbated or ameliorated due to the relationship between posterior fossa and brain (cerebellum) volume. Although the natural course of asymptomatic pediatric Chiari type 1 malformation with or without syringomyelia is more favorable than that previously acknowledged (19), patients treated with GH replacement therapy should be followed closely with serial imaging and clinical assessments for evidence of progression. High doses of GH could be used for patients with Chiari type 1 malformation, if followed by careful monitoring of head MRI.

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