Juvenile Muscular Atrophy of a Unilateral Upper Extremity (Hirayama Disease) in a Patient with CHARGE Syndrome

T. Yagihashi^a K. Hatori^{d,e} K. Ishii^b C. Torii^a S. Momoshima^c T. Takahashi^a
K. Kosaki^a

Departments of ^aPediatrics, ^bOrthopaedic Surgery and ^cRadiology, Keio University School of Medicine,
^dDepartment of Rehabilitation Medicine, Juntendo University School of Medicine, and ^eDepartment of Neurology,
Koto Hospital, Tokyo, Japan

Key Words

CHARGE syndrome • *CHD7* • Hirayama disease

Abstract

CHARGE syndrome is an autosomal dominant congenital anomaly syndrome, and the causative gene is *CHD7*. We report a patient with a *CHD7* mutation who presented with juvenile muscular atrophy of a unilateral upper extremity, a presumably heterogeneous condition that is also known as Hirayama disease. This association has not been previously described. Weakness and atrophy of the hands should be carefully examined in patients with CHARGE syndrome, since Hirayama disease might be a possible complication in adolescent patients with this syndrome.

Copyright © 2010 S. Karger AG, Basel

CHARGE syndrome is characterized by choanal atresia and/or cleft lip/palate, ocular colobomas, cardiovascular malformations, retardation of growth, ear anomalies, and deafness [Pagon et al., 1981; Aramaki et al., 2006]. It is caused by the heterozygous mutation of the *CHD7* gene, which encodes the chromodomain helicase DNA-binding protein [Vissers et al., 2004]. Recent advances in pediatric cardiac technology, earlier diagnosis

and improved intensive care have allowed children with CHARGE syndrome to survive into adulthood. However, adolescent or adult phenotypes of CHARGE syndrome have not yet been well characterized. Here, we report a patient with CHARGE syndrome who presented with a previously undescribed complication: juvenile muscular atrophy of a unilateral upper extremity, also known as Hirayama disease.

Juvenile muscular atrophy of a unilateral upper extremity is a rare musculoskeletal disorder characterized by weakness and atrophy of the distal upper limbs. The onset of this disorder corresponds to the beginning of the adolescent growth spurt [Hirayama and Tokumaru, 2000]. The etiology of Hirayama disease is unknown but is likely heterogeneous. Subgroups of patients with Hirayama disease have occurred within families [Sobue et al., 1978; Schlegel et al., 1987; Tandan et al., 1990; Nalini et al., 2004], and an OMIM number has been assigned (No. 602440). Hirayama disease was originally described as ‘juvenile muscular atrophy of a unilateral upper extremity’. The clinical features of Hirayama disease include an occurrence between 15 and 25 years of age; the insidious onset of unilateral or asymmetric oblique amyotrophy; an association with fine tremulous irregular involuntary movements of the fingers on moderate extension or fasciculation in the extensors of the forearm; a nonpro-

gressive course and disease arrest within a few years after onset; and the absence of sensory findings, reflex changes in the arms and pyramidal signs in the legs. Although the pathogenesis of the disorder is uncertain, current hypotheses include recurrent damage from a compressive myelopathy, a neurodegenerative focal motor neuron disorder and focal myelopathy with spinal cord ischemia.

A 30-year-old Japanese man with multiple congenital anomalies was referred to our genetics clinic. He was born by spontaneous vaginal delivery at 38 weeks of gestation after an unremarkable pregnancy. The parents were nonconsanguineous and phenotypically normal. His birth weight was 2,610 g. At birth, he was found to have bilateral choanal atresias, torticollis, dysmorphic ears, a coloboma of the right choroid, and undescended testes. Because of asphyxia neonatorum and subsequent feeding difficulties, he was hospitalized for 9 months. He had no cardiac or renal malformations.

He exhibited postnatal growth retardation and a developmental delay; his height corresponded to the third percentile. He walked alone at the age of 23 months. At the age of 3, an ABR examination revealed a hearing loss: 78 dB on the right side, and 64 dB on the left side. He had minimal verbal expression and communicated with his parents and peers using sign language and writing. During early childhood, he had multiple episodes of infections, including recurrent bronchitis, conjunctivitis and otitis media requiring a tympanotomy. At the age of 6 years, he developed a bilateral inguinal hernia and underwent surgery. Throughout childhood, his written and sign language abilities progressed but remained moderately delayed, despite the use of hearing aids.

He attended a school for speech-handicapped children beginning at the age of 6 years. At the age of 13, he initially experienced a transient episode of right elbow pain. With 16, he experienced a residual weakness and atrophy of the right hand with an insidious progression. At 17, he was referred to an orthopedic specialist. Supportive therapy, including cervical collar therapy and physiotherapy, was partially effective, and he was able to get a data entry job at the age of 18 years. Also, at the same time, his vision deteriorated with metamorphopsia. An ophthalmological examination revealed bilateral retinal breaks associated with retinochoroidal colobomas, and he subsequently underwent laser treatment.

A physical examination performed at the age of 30 years revealed a weight of 51 kg, a height of 151.0 cm (<3rd centile) and a head circumference of 53.0 cm (<3rd centile). He had an asymmetric face with facial nerve palsy, a triangular-shaped antihelix, focal alopecia, a low hair

line, moderate scoliosis, a hockey-stick palmar crease, and an accessory nipple. The length and configuration of the penis was normal. The genitals were normal with bilaterally descended testes of normal size, which had been corrected by a bilateral orchiopexy for the undescended testes. His sense of smell was reportedly normal. Because of his hearing loss, his verbal communicative skills were severely impaired. However, he had a good comprehension of written and sign language. His mental development, as evaluated using the Raven's Progressive Matrices test (an intelligence test developed for patients with hearing loss), corresponded to that of an average Japanese 9-year-old [Raven et al., 1993].

A neurological examination revealed a tremor of the right hand accompanied by marked atrophy of the right hand and forearm (fig. 1, left). The circumferences of his forearms were 21.5 cm (right) and 23.6 cm (left). His total hand lengths were 16.2 cm (right) and 17.1 cm (left), respectively. His palmar lengths were 9.2 cm (right) and 9.7 cm (left), respectively (fig. 1, right). An examination showed a mild weakness of the right hand and distal forearm muscles. His right finger extension was slightly limited. No sensory deficits in response to pain or temperature were noted. He had 4 major findings (ocular coloboma, choanal atresia, cranial nerve anomaly, and characteristic ear anomaly) and 3 minor findings (distinctive facial features, growth deficiency and developmental delay) meeting the diagnostic criteria for CHARGE syndrome [Blake et al., 1998]. His G-banded karyotype was normal. High-performance liquid chromatography DNA screening and direct sequencing identified one heterozygous mutation at codon 6,148, converting an arginine (CGA) into a stop codon (TGA) in exon 31 of the *CHD7* gene [Aramaki et al., 2006].

Asymmetry of the face is a relatively frequent feature of CHARGE syndrome, but unilateral atrophy of the upper arm has not been previously described. The above-mentioned neurological features were compatible with a clinical diagnosis of Hirayama disease: (1) onset during adolescence, (2) insidious onset of unilateral amyotrophy, (3) tremors of the fingers, and (4) nonprogressive course and disease arrest within a few years after onset [Hirayama and Tokumaru, 2000]. MRI cervical spine flexion views revealed the cardinal features of Hirayama disease [Hirayama and Tokumaru, 2000; Chen et al., 2004; Misra et al., 2005; Badve and Pruthi, 2009]: (1) anterior displacement of the posterior dural sac, (2) effacement of the cerebrospinal fluid space with multiple flow voids and (3) atrophy of the spinal cord. Anterior displacement of the dural sac was present from C6 to C7, and the concomitant

Fig. 1. Muscular atrophy of the right hand at the age of 30 years. Left, Muscular atrophy can be seen in the right hand and forearm muscles. Atrophy is predominant on the ulnar side, especially in the hypothenar muscles (arrow). Right, Note the asymmetry of the hands. The circumferences of his forearms were 21.5 cm (right) and 23.6 cm (left). His total hand lengths are 16.2 cm (right) and 17.1 cm (left). His palmar lengths are 9.2 cm (right) and 9.7 cm (left).

enlargement of the posterior epidural venous plexus was depicted as multiple flow voids (fig. 2, top left and middle). The axial views revealed a flattened, kidney-shaped spinal cord with a concavity on its ventral surface, whereas a normal cord appears oval in shape with a convex ventral surface. Moreover, the atrophy of the spinal cord was more prominent on the right side, of which the limb was affected clinically (fig. 2, right).

We here reported a patient with molecularly confirmed CHARGE syndrome who exhibited the clinical and radiological features of Hirayama disease. The lack of previous reports on this specific combination of these 2 relatively rare conditions might indicate that their association occurred by chance. Alternatively, Hirayama disease might have occurred secondary to the craniovertebral defects in this patient with CHARGE syndrome. A mechanical hypothesis has been proposed as a possible mechanism for the spinal defects in Hirayama disease: sustained or re-

peated neck flexion might cause an anterior shift of the cervical dural sac, with the subsequent compression of the cervical cord at that segment increasing the intramedullary pressure, resulting in a microcirculatory disturbance in the anterior horn [Hirayama and Tokumaru, 2000]. Epidemiological studies support this notion because cervical kyphosis is a known risk factor for Hirayama disease [Chen et al., 2004]. We suspect that the Hirayama disease phenotype in the propositus might be ascribed to the cervical kyphosis that occurred as part of the craniovertebral defects. The clinical significance of the association between CHARGE syndrome and Hirayama disease will require further validation in another patient. Nevertheless, based on general observations of vertebral malalignment (e.g. scoliosis and kyphosis [Doyle and Blake, 2005]), asymmetry of the hands or forearms might represent a useful clinical sign indicating the presence of a potentially treatable complication, Hirayama disease.

Fig. 2. Left, Midline sagittal T2-weighted MRI of the cervical spine in a neutral position reveals focal atrophy of the spinal cord at the C6–7 vertebral levels (arrows). The posterior wall of the dural sac is in close contact with the spinal canal. Middle, Midline sagittal T2-weighted MRI of the cervical spine with neck flexion reveals anterior displacement and marked flattening of the spinal cord at the C6–7 levels (arrow), with an enlarged posterior epidu-

ral venous plexus with small flow void signals inside (arrowhead). Right, Axial T2-weighted MRI of the cervical spine at the C6–7 vertebral levels reveals kidney-shaped spinal cord atrophy, especially on the right side, and anterior displacement of the spinal cord with concomitant enlargement of the posterior epidural venous plexus (arrow).

In summary, a patient with a *CHD7* gene mutation in the CHARGE-syndrome-critical region presented with the typical clinical course of Hirayama disease. These findings suggested that Hirayama disease might be a possible complication of CHARGE syndrome in adolescent patients.

Acknowledgement

We would like to thank the Contract grant sponsors: The Ministry of Health, Labour, and Welfare of Japan.

References

- Aramaki M, Udaka T, Kosaki R, Makita Y, Okamoto N, et al: Phenotypic spectrum of CHARGE syndrome with *CHD7* mutations. *J Pediatr* 148:410–414 (2006).
- Badve C, Pruthi S: Hirayama disease. *Pediatr Radiol* (2009), E-pub ahead of print.
- Blake KD, Davenport SL, Hall BD, Hefner MA, Pagon RA, et al: CHARGE association: an update and review for the primary pediatrician. *Clin Pediatr (Phila)* 37:159–173 (1998).
- Chen CJ, Hsu HL, Tseng YC, Lyu RK, Chen CM, et al: Hirayama flexion myelopathy: neutral-position MR imaging findings-importance of loss of attachment. *Radiology* 231:39–44 (2004).
- Doyle C, Blake K: Scoliosis in CHARGE: a prospective survey and two case reports. *Am J Med Genet A* 133A:340–343 (2005).
- Hirayama K, Tokumaru Y: Cervical dural sac and spinal cord in juvenile muscular atrophy of distal upper extremity. *Neurology* 54: 1922–1926 (2000).
- Misra UK, Kalita J, Mishra VN, Kesari A, Mittal B: A clinical, magnetic resonance imaging, and survival motor neuron gene deletion study of Hirayama disease. *Arch Neurol* 62: 120–123 (2005).
- Nalini A, Lokesh L, Ratnavalli E: Familial monomelic amyotrophy: a case report from India. *J Neurol Sci* 220:95–98 (2004).
- Pagon RA, Graham JM Jr, Zonana J, Yong SL: Coloboma, congenital heart disease, and choanal atresia with multiple anomalies: CHARGE association. *J Pediatr* 99:223–227 (1981).
- Raven JC, Court JH, Raven J: Manual for the Raven's Coloured Progressive Matrices. Nihon Bunka Kagakusha, Tokyo (1993).
- Schlegel U, Jerusalem F, Tackmann W, Cordt A, Tsuda Y: Benign juvenile focal muscular atrophy of upper extremities – a familial case. *J Neurol Sci* 80:351–353 (1987).
- Sobue I, Saito N, Iida M, Ando K: Juvenile type of distal and segmental muscular atrophy of upper extremities. *Ann Neurol* 3:429–432 (1978).
- Tandan R, Sharma KR, Bradley WG, Bevan H, Jacobsen P: Chronic segmental spinal muscular atrophy of upper extremities in identical twins. *Neurology* 40:236–239 (1990).
- Vissers LE, van Ravenswaaij CM, Admiraal R, Hurst JA, de Vries BB, et al: Mutations in a new member of the chromodomain gene family cause CHARGE syndrome. *Nat Genet* 36:955–957 (2004).