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

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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.

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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 hairline, 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
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 repeated 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.
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.

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