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Symmetric Atrophy of Bilateral Distal Upper Extremities and HyperIgEaemia in a Male Adolescent With Hirayama Disease

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Hirayama disease is a rare neuromuscular disorder with peak age of onset at 15 to 17 years among young males. We report a male adolescent presenting with symmetric weakness and atrophy of bilateral upper extremities progressing for 2 years before stabilizing. Otherwise, he did not complain of any sensory disturbance. Electrophysiological findings revealed motor neuron damage at the C7-T1 spinal segments. Cervical magnetic resonance imaging revealed a high-signal mass of posterior dural sac at the C5-T5 vertebral level during neck flexion. Specifically, he had elevated serum total

immunoglobulin E level, which had been postulated to be a precipitating factor in Hirayama disease. Early recognition and intervention of this unique neuromuscular disorder is important to avoid ongoing damage to motor neurons. Through this report, we would like to emphasize the crucial role of a pediatric neurologist in averting the progression of Hirayama disease at an early stage.

Keywords: atrophy; flexion myelopathy; hyperIgEaemia; Hirayama disease

Juvenile muscular atrophy of the distal upper extremity or Hirayama disease is a rare neuromuscular disorder that mostly affects male adolescents with predominantly unilateral involvement of the upper extremity.¹ Until now, the pathogenic mechanism of Hirayama disease remains unknown. It was first recognized by Hirayama et al in 1959, and the majority of cases have mainly been encountered in Japan, with the exception of occasional reports from Singapore, Taiwan, Hong Kong, Nigeria, Denmark, Holland, United States, Austria, United Kingdom, France, Canada, Poland, and Germany.^{2,3} However, reports from pediatricians are quite rare,³ although

the peak onset age ranges from 15 to 17 years. Clinically, weakness and atrophy of the upper extremities usually progress insidiously over several years during adolescence and become remarkable at early adulthood.² Thus, early recognition and intervention of this unique neuromuscular disorder by a sufficiently experienced pediatrician is crucial to avert ongoing damage to motor neurons. Here we report a male adolescent with atypical clinical features of Hirayama disease onset since 13 years of age, which was then diagnosed successfully through serial neuroimaging and electrophysiological studies.

Case Report

A 15-year-old male adolescent came to our outpatient department because of progressive atrophy and weakness of bilaterally distal upper extremities during the previous 2 years. Claw hands and trembling of the fingers while stretching out his hands were observed. He denied having trauma of his head, neck, and upper extremities previously. The weakness progressed insidiously and became remarkable recently. He had difficulties in grasping, lifting objects, and making delicate hand movements in daily life. Weakness was not exacerbated by a cold environment. He did not have neck pain or soreness. The movements of the neck were not limited. He denied any sensory

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Figure 1. Clinical pictures of a male adolescent with Hirayama disease. A and B, Claw hands and muscular atrophy in the bilateral forearms presented predominantly when the patient raised his upper extremities. C, Symmetric atrophy of bilateral intrinsic hand and forearm ulnar-sided muscles except for brachioradialis characterize a picture of oblique atrophy.

symptoms or paresthesia. His family history was negative for neurodegenerative or neuromuscular disease, and there was no evidence of consanguinity.

On examination, muscular wasting presented symmetrically at bilateral intrinsic muscles of the hands and the ulnar sides of the forearms with sparing of brachioradialis, giving a picture of claw hand and “oblique atrophy” (Figure 1). The muscle strength of the distal upper extremities decreased ($2-3 \pm 5$) symmetrically. The sensation and muscle tone were normal and deep tendon reflexes were well preserved. Babinski reflexes revealed plantar flexion. There was no clonus or fasciculation. Superficial abdominal reflex was intact. Besides, the lower extremities were not involved.

Serum creatine kinase and lactate were normal. No elevation of serum lead level was noted. Genetic studies showed neither deletion of survival motor neuron 1 (*SMN1*) gene nor CAG trinucleotide repeat expansion on the X chromosome (repeat number = 20; normal < 40).

Total serum immunoglobulin E level was elevated (415 IU/mL; normal range, 66.4-109 IU/mL), with negative multiple allergosorbent chemiluminescent assay. Otherwise, completed blood examination showed no elevated eosinophilic leucocytes. The patient’s allergic history was retrieved but was unremarkable. Nerve conductive velocity showed low-amplitude compound muscle action potentials of bilateral median motor (right: 3.1 mV; left: 1.4 mV) and ulnar motor nerves (right: 0.2 mV; left: 0.3 mV) and slow velocities of left ulnar motor nerve (37 m/s; normal: 51-58 m/s). Delay of F-wave latency over right ulnar and median nerves (35.1 and 40.2 ms, respectively) was found. Needle electromyography (EMG) revealed loss of motor unit potentials, replaced by rapid firing, high-amplitude, and polyphasic waves at bilateral flexor carpi radialis, triceps, extensor digitorum, first dorsal interosseous, and abductor pollicis brevis muscles, which indicated marked axonal denervation–reinnervation change over C7-T1 myotomes.

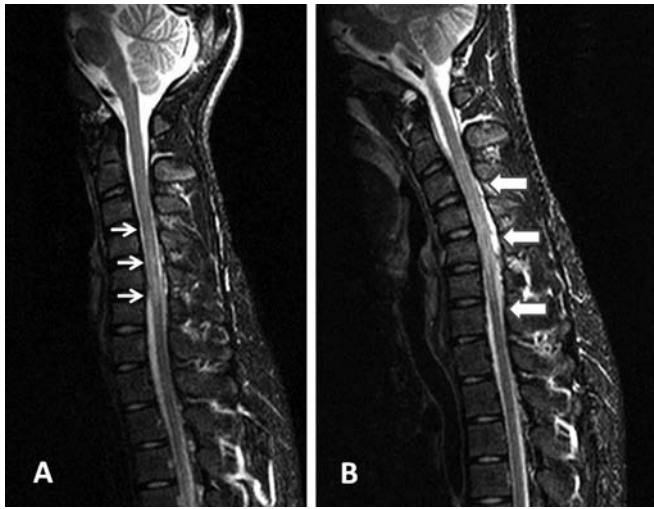


Figure 2. A, The T2-weighted cervical magnetic resonance imaging (MRI) showed cord flattening and intramedullary hyperintensities at the C4-C6 spinal cord (arrows) in neutral cervical position, which is indicative of gliosis in the atrophied segment of the spinal cord. B, High-signal crescent-shaped structures at C5-T5 epidural space (solid arrows) appeared when the patient fully flexed his neck.

Cervical spine radiographs showed no misalignment of the vertebral bodies in the flexed neck position. Cervical computed tomography (CT) showed narrowing of the C3-C6 spinal canal and enhanced tortuous tubular structures at C5-T5 spinal cord after contrast injection. Neutral-position cervical T2-weighted magnetic resonance imaging (MRI) revealed myelopathic changes at the C4-C6 spinal cord (Figure 2A). Furthermore, under T2-weighted and postenhancement T1-weighted imaging with the neck under full flexion, we observed the posterior dural sac of the C5-T5 level of spinal cord was shifted anteriorly causing compression to the corresponding spinal cord level (Figure 2B). Dural arteriovenous malformation in the canal of the cervicothoracic spine was suspected but subsequently excluded by negative cerebral angiographic findings.

Combining clinical presentations, electrophysiology and neuroimaging findings were consistent with the diagnosis of Hirayama disease. Prevention of ongoing spinal cord damage by avoiding strenuous neck flexion and usage of a neck collar were recommended. At the 1-year follow-up, he showed no progression of atrophy and weakness. Repeated cervical MRI revealed neither deteriorating damages at C4-C6 spinal cord nor progressive enlargement of the posterior spinal dural sac. Interestingly, a decline in the serum IgE level (234.0 IU/mL) was observed, which also suggested a stabilizing course may be expected.

Discussion

Hirayama disease is a rare neuromuscular disorder characterized by muscle weakness and atrophy confined

focally to the distal upper extremities.^{2,4} It usually affects young male adolescents, with a peak age of 15 to 17 years. Presumably because of this age distribution, a pediatric specialist would be the first physician encountering this disorder during clinical practice because the earliest onset symptoms have been reported at 3.5 years of age.⁵ Our patient presented with an insidious onset of symmetric atrophy over both forearms and shared several features compatible with lesions of the lower motor neurons, such as those involving myotomes showing low-amplitude compound muscle action potentials and delay of F-wave latency of nerve conductive velocity, and giant motor unit potentials of EMG,² but somehow it differs because of its nonprogressive behavior. However, this disorder can also be readily differentiated from other motor neuron disorders via various manners, such as Kugelberg-Welander disease and Kennedy syndrome by genetic testing, juvenile amyotrophic lateral sclerosis by lack of pyramidal signs, and other spinal cord-occupying lesions by spinal MRI or angiogram.⁴ Fatigue, weakness, tremors, and neck soreness usually presented as the first symptoms and onset insidiously for years.⁴ Muscular wasting affects predominantly over the ulnar sides of the forearms with sparing of brachioradialis, characterize a picture of oblique amyotrophy. Atrophy is unilateral, specifically on the right-hand side in most patients (72.1%), asymmetrically bilateral in some (24.8%), but symmetrical, as seen in our case, is extremely rare, only accounting for 3.1%.³ Exacerbating weakness on exposure to a cold environment (cold paresis) was absent in our patient although it has been regarded as a distinct feature in more than 90% of cases.

The pathogenesis of Hirayama disease remains vague. This disorder is mostly nonfamilial and so far, no responsible gene has been identified. The most tempting postulation of pathogenesis is flexion myelopathy due to dynamic spinal cord compression by forward displacement of vertebral posterior dural sac during neck flexion.^{2,3} It is further supported by characteristic neuroimaging presenting a high-signal crescent-shaped lesion especially at the C5-T1 posterior epidural space, which is best seen under T2-weighted or postenhancement MRI with neck flexion.^{4,6} The neutral-position cervical MRI is usually normal, although lower cord atrophy, asymmetric cord flattening, and intramedullary hyperintensity on T2-weighted imaging are rarely observed,^{6,7} as seen in our patient. Another supporting feature suggests that the predisposed age distribution may be associated with disproportional length between the vertebral column and spinal canal contents (former > latter) during the period of juvenile growth spurt, which results in consequently limited extension of the dura mater during neck flexion.^{2,6} Otherwise, no histopathological abnormality of the dura mater has been reported.² Even so, although the theory of developmental imbalance may explain cessation of disease progression after puberty in most cases, there are still

arguments about its predilections in the male gender, its higher prevalence in the Asian population, and the fact that 13% to 29% of patients develop typical symptoms/signs without any evidence of neuroimaging abnormalities.^{3,7}

Casual findings reveal up to 70% of cases of Hirayama disease have atrophic diatheses or hyperIgEaemia.^{8,9} Intriguingly, the atrophy-associated postulation seems to be more defensible in pathogenesis because some epidemiological studies have demonstrated that allergic disorders affect young people more than elderly people, males more than females, and Asians more than non-Asians.¹⁰ Relation of motor neuron damage with immunoglobulin E-mediated platelet activation and arterial spasms has been raised.⁸ Serum immunoglobulin E concentrations were higher in patients with a disease duration of less than 5 years, so it might predict clinical severity especially in the early stage of the disease.⁹

A self-limited course is expected in most cases because weakness and atrophy usually arrest within 5 years after initial progression.^{2,4} The treatment is usually conservative. Wearing a neck collar for an average duration of 3 to 4 years is suggested to prevent further motor neuron damage.² Another field of therapeutics that may be explored is based on the theory of atrophic correlation to this disease. Certainly, plasma exchange has been applied to treat patients with Hirayama disease successfully⁸ but so far this remains controversial because of the concern of potential complications. Besides, suppression of serum immunoglobulin E may be potentially therapeutic in the future, especially in the early phases of the disease.⁹

In conclusion, we emphasize Hirayama disease is definitely a neurological disorder in pediatrics because of its peak age of onset during adolescence. Particularly in young male adolescents with distal upper extremity weakness, atrophy, preserved reflexes, and normal sensory examination, Hirayama disease should always be considered. Timely diagnosis by a sufficiently experienced pediatric neurologist is imperative so that early interventions

can prevent progressive damage to spinal motor neurons and minimize functional disability.

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