Early-onset Hirayama disease in a female

Matthias Baumann1, Josef Finsterer2, Elke R Gizewski3 and Wolfgang N Löscher4

Abstract
Objectives: Hirayama disease is a rare myelopathy, occurring predominantly in males with onset in the teens.
Methods and results: Here, we report a young female patient who developed the first signs of Hirayama disease at 10.5 years of age. Prior to onset, she had experienced a growth spurt and grew about 8 cm. The disease progressed over 3 years and the typical clinical, electrophysiological, and neuroimaging signs of Hirayama disease were found. After this period and achievement of her final height, no further progression was noticed.
Conclusions: This case highlights that pediatric neurologists should be aware of Hirayama disease, which can also occur in girls in early adolescence.

Keywords
Hirayama disease, motor neuron disease, myelopathy, magnetic resonance imaging, nerve conduction

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Introduction

Hirayama disease (HD) or juvenile muscular atrophy of distal upper extremity (JMADUE) is a rare myelopathy, occurring predominantly in males.1 HD is characterized by juvenile-onset asymmetric and painless amyotrophy of the distal upper limbs due to affection of the cervical segments C7, C8, or T1.1 Early-onset HD in a female, as in the following case, has been only rarely reported.2–4

Case report

The patient is a 17-year-old Caucasian female who developed symptoms in the upper extremities insidiously starting at the age of 10.5 years. Initially, she had only mild difficulties in extending the left index finger and 1 year later also in extending the right middle finger. At the age of 12 years, more obvious weakness of the hands, predominantly on the left side, developed. Weakness increased in cold weather and the hands were often cold and sweaty. No sensory deficit was noticed. The history for cervical trauma was negative but in the year before onset she experienced a growth spurt and grew about 8 cm (between 75th and 90th centile for growth velocity). The family history was negative for neuromuscular disorders.

Neurological examination at the age of 13 years revealed marked weakness (MRC 2 to 3–) for extension of the index and middle fingers bilaterally and for abduction of the left thumb (Figure 1(a)–(c)). Additionally, there was weakness (MRC 3+ to 4) for extension of the ring and little fingers bilaterally, for abduction of the right thumb, and for abduction and adduction of the left fingers II–V, and flexion of the left fingers II–V. Postural tremor and poly-mini-myoclonus of the fingers on extension could be seen. There was marked wasting of the right thenar and mild wasting of other intrinsic hand muscles. Muscle strength of wrist flexion and extension, pronation, and supination of the forearms, flexion and extension of the elbow, and of abduction in the shoulder was normal. Sensory deficits were absent and deep tendon reflexes were intact. Neurological examination of the lower extremities was normal. Motility of the cervical spine and forward flexion of the whole spine were normal.

A pure motor deficit affecting roots C7 to T1, more

1Clinical Department of Pediatrics I, Division of Pediatric Neurology, Medical University of Innsbruck, Innsbruck, Austria
2Krankenanstalt Rudolfstiftung, Vienna, Austria
3Department of Neuroradiology, Medical University of Innsbruck, Innsbruck, Austria
4Department of Neurology, Medical University of Innsbruck, Innsbruck, Austria

Corresponding Author: Josef Finsterer, Krankenanstalt Rudolfstiftung, Postfach 20, 1180 Vienna, Austria.
Email: fifigs1@yahoo.de
pronounced on the left than on the right side, was diagnosed. At the age of 13 years, her height was 175 cm (5 cm above 97th centile), and her weight was 58 kg (75th–90th centile). At the age of 14 years (Figure 1(d) and (e)), the pattern of weakness and wasting was unchanged but severity of weakness had slightly increased, being stable during the last 6 months. At further follow-up examinations during the following years no further change of the pattern and extent of weakness or wasting was recognized.

Nerve conduction studies of the median and ulnar nerves showed reduced compound motor unit action potentials (MUAPs) and a slightly reduced motor conduction velocity on the left side. No conduction blocks were found and sensory nerve conduction studies of the median, ulnar, and radial nerves were normal. Nerve conduction studies of the right peroneal nerve were normal. Needle electromyography of the first, left interosseus muscle showed high-amplitude, long-duration MUAPs indicating chronic denervation. Magnetic resonance imaging (MRI) of the cervical spine in an orthotopic head position (Figure 1(f)) and under head anteflexion (Figure 1(g) and (i)) showed flattening and a slight intramedullary signal alteration of the myelon between segments C5 and C7. Anti-ganglioside antibodies, including anti-GM1 IgM antibodies, indicating multifocal motor neuropathy, were absent. Although HD was suspected, a trial with intravenous immunoglobulin (IVIG; 2 g/kg bodyweight over 3 days) was carried out since IVIG-responsive motor neuropathies without conduction block have been reported. Since IVIG were ineffective, they were discontinued. During the following years, symptoms did not progress further supporting the diagnosis of HD. She was recommended to wear a cervical collar but only used it for a short period.

Figure 1. (a–c) Neurological examination at the age of 13 years shows marked weakness on extension of the index and middle finger on both sides and on abduction of the left thumb. At the age of 14 years, (d and e) the pattern of the weakness has not changed; the weakness is bit more pronounced, but has been stable in the last 6 months. (c and e) Marked atrophy of the right thenar and to a lesser degree of the other intrinsic hand muscles can be seen. Spinal MRI (T2-weighted images) at the age of 14 years shows flattening of the lower cervical cord at vertebral levels C5 to C7 on sagittal images in neutral position (f) with a spinal canal anterior-posterior diameter of 9.5 mm and in neck flexion (g) with a spinal canal diameter of 7.3 mm measured at C6/7. On axial images in neck flexion (i, at level C5/C6), the anterior-posterior diameter of the lower cervical myelon is diminished to less than 5 mm. (g and i) Also a slight signal hyperintensity in the ventral myelon can be seen extending from vertebral levels C5 to C7. (h) On the axial image at a higher vertebral level (C3/C4), no abnormality of the cord can be seen.
Discussion

The presented patient is interesting because she is a female and onset was early. She showed typical clinical, electrophysiological, and radiological manifestations of HD with asymmetric distal upper extremity weakness and muscular atrophy affecting segments C7-T1. Symptoms started insidiously and gradually progressed over 3 years before they stabilized. She showed tremor and poly-mini-myoclonus of the fingers on extension, worsening of the weakness with exposure to cold, and no sensory deficits.

HD has been mainly reported from Asia, with fewer case reports from Europe and North America.2,6 It usually affects young males with onset from adolescence to early adulthood. Large series confirm this male preponderance and age of onset (China: n = 192, m:f = 7:1, mean age of onset 16.8 years; Japan: n = 333, m:f = 8:1, mean age of onset in males 17.6 years and in females 19.3 years).8 Clinical features of the presented patient are very similar to previous reports. It therefore seems that HD in females is clinically indistinguishable from HD in males. However, the early onset in a female, as in our case, has rarely been reported.2–4

Concerning the etiology, it was proposed that a disproportionate growth of the vertebral column and the contents of the spinal canal during the juvenile growth spurt cause HD and the peak of the histogram for onset age is approximately 2 years later than the peak of growth curve.1 So far, however, this theory remains to be proven. A growth spurt was also found in the present patient 1 year prior to onset of symptoms and she is tall for her age. Disproportionate growth of the vertebral column and the spinal cord may result in distension of the spinal cord and relative shortening of the dorsal roots and loss of attachment between the posterior dural sac and the subjacent lamina.1 Under physiologic conditions, neck flexion results in an increase in the overall length of the vertebral canal, the loosely suspended dural sac is stretched but remains abutting the walls of the spinal canal. In HD, on the contrary, the dural sac becomes shorter in length and is tighter already in the neutral position because of the differential growth rates of the vertebral canal and the dura. As a consequence, neck flexion causes detachment of the tight dura from its posterior anchor and the dura falls forward and causes abutment of the spinal cord against the anterior vertebral column.1,4,8 Additionally, neck flexion in HD patients results in dysfunction of anterior horn cells, as has been recently demonstrated in a study of 38 HD patients showing an increased number of repeater F-waves during neck flexion.9 The authors concluded that HD patients should avoid neck flexion for a long period of time.9

Male preponderance of HD may be explained by different growth rates and different anatomy between males and females. The peak of growth velocity curve in females is approximately 2 years earlier than in males.1 In a nationwide survey in Japan, onset of HD was slightly later for females (mean, 19.3 years) than for males (17.6 years).8 It was speculated that this difference in age of onset might be due to the fact that once males begin to increase in height, they increase quickly and eventually exceed the height of females.8 Further studies would be useful to verify how an accelerated pubertal growth spurt is related to the occurrence of HD. An earlier pubertal growth spurt onset seems to be related to a higher peak height velocity,10 suggesting that HD patients have an earlier onset of their pubertal growth spurt.

Concerning the early diagnosis of HD, it has been recently reported that the ratio amplitude of the compound muscle potential (CMAP) of the ulnar nerve to the median CMAP amplitude is significantly decreased in HD patients as compared to patients with amyotrophic lateral sclerosis (ALS).11 A further electrophysiological technique to differentiate between HD and ALS at an early stage is repetitive nerve stimulation.12 In a study of 33 HD and 37 ALS patients, it has been demonstrated that repetitive nerve stimulation showed a decrement in proximal nerves in 73% of the ALS patients but in none of the HD patients.12

Treatment of HD has been addressed in only a few reports, but in some of them, a beneficial effect of wearing a cervical collar or of undergoing physiotherapy has been demonstrated.13 Avoiding of neck flexion over a long period of time is another non-surgical treatment option.9 Recently, several studies showed a promising beneficial effect of multilevel anterior cervical discectomy with fusion and plate fixation.14,15

It is concluded that pediatric neurologists should be aware of HD and that HD also occurs in girls in early adolescence. Clinical presentation of HD is not at variance between female and male patients but onset of the clinical manifestations in females may be earlier than usual.

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All authors contributed equally.

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