A Clinical, Magnetic Resonance Imaging, and Survival Motor Neuron Gene Deletion Study of Hirayama Disease

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Background: Hirayama disease (HD) is a segmental non-progressive spinal muscular atrophy found in male patients.

Objective: To report the results of a comprehensive evaluation of clinical, magnetic resonance imaging (MRI), electromyography (EMG), and survival motor neuron (SMN) gene analysis of HD.

Design: Clinical, MRI, and SMN gene deletion study.

Setting: Tertiary care teaching hospital.

Patients: Patients with HD diagnosed according to defined criteria were included in the study.

Interventions: Patients underwent a neurologic evaluation and pedigree charting. Concentric needle EMG was performed on a number of muscles. Motor nerve conduction study of the median, ulnar, and peroneal nerves and sensory conduction study of the median, ulnar, and sural nerves were also performed. Spinal MRI of the cervical region was performed with the 2-T scanner operating at 1.5 T. Gene deletion study of SMN1 and SMN2 was performed in all patients.

Main Outcome Measures: History of trauma, occupation, exercise, associated medical disease, and cold paresis and muscle wasting, power, reflex changes, and tone.

Results: Fifteen male patients with HD from 14 families participated in the study (mean age at the onset of disease, 18 years; range, 15-23 years). Muscle weakness and wasting were noted in the right upper limb in 12 and the left upper limb in 3, which became bilateral in 8 patients. Cold paresis was present in 6 patients and polymyoclonus in all patients. The EMG revealed fibrillations in 10, fasciculations in 15, and neurogenic motor unit potentials in C7, C8, and T1 myotomes in all patients. The EMG abnormalities were unilateral in 5, bilateral in 10, and subclinical in 2 patients. Spinal MRI revealed cord atrophy in 3 of 11 patients. Although family history was present in 1 brother only, the results of both SMN1 and SMN2 gene deletion studies were negative in all patients.

Conclusions: The SMN gene deletion is not found in HD. Exclusive occurrence in male patients and the presence of this disease in 2 brothers suggest a possible role of the X chromosome, which needs further evaluation.

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Nonprogressive juvenile spinal muscular atrophy (SMA), also known as Hirayama disease (HD), is characterized by insidious onset of unilateral or asymmetric oblique amyotrophy that affects the C7, C8, and T1 myotomes. It usually affects young men and is characteristically associated with aggravation of weakness on exposure to cold, known as cold paresis. The onset is insidious and characterized by muscle weakness and atrophy in the hand and forearm with sparing of brachioradialis, giving the characteristic appearance of oblique amyotrophy. The amyotrophy is unilateral in most patients and asymmetrically bilateral in some. Although there are no fasciculations at rest, finger extension causes fascicular twitching or polymyoclonus. The initial progressive course of HD is followed by spontaneous arrest within several years after onset. The patients with HD have been reported mainly from Japan but also from Denmark, Holland, Singapore, the United States, India, Malaysia, Sri Lanka, and France.1-5 Spinal muscular atrophies are clinically and genetically heterogeneous, and their primary cause remains unknown.6 Using linkage analysis, the locus was mapped to chromosome 5q11.2-13.3, which was shown to be associated with SMA.7 Recent studies have shown that the deletion of the small subregion of 5q13 is associated with phenotypic expression.
of the SMA. These findings have resulted in the identification of 2 candidate genes: the survival motor neuron (SMN) gene and the neuronal apoptotic inhibitory protein (NAIP) gene. Hirayama disease has been attributed to several factors, including trauma, ischemia, autoimmune basis, familial or hereditary occurrence, and toxins and infections.

In SMA types 1, 2, and 3, variable frequency of the SMN gene deletion has been reported. Absence of the SMN gene deletion has been reported in 2 patients with upper limb distal SMA (HD) from Italy. A comprehensive evaluation of clinical, magnetic resonance imaging (MRI), electromyography (EMG), and genetic analysis may help in understanding HD better. Although different aspects have been reported in various studies, a comprehensive evaluation is lacking. This article reports the results of clinical, neurophysiologic, MRI, and SMN gene analysis of 15 patients with HD.

**METHODS**

This study was conducted in a tertiary care teaching hospital in India. The basis of diagnosis of HD was as follows: (1) occurrence between 15 and 25 years of age; (2) insidious onset of unilateral or asymmetric oblique amytrophy often associated with cold paresis; (3) association with fine tremulous irregular involuntary movements of the fingers on moderate extension or fasciculations in the extensors of forearm; (4) absence of sensory findings, reflex changes in arms, little if any pyramidal signs in the legs, and absence of ocular or sphincter disturbances; (5) nonprogressive course and arrest of disease within a few years after the onset; and (6) laboratory data that indicate neurogenic changes in EMG restricted to C7, C8, and T1 myotomes and normal nerve conduction study results.

A detailed history and clinical examination were performed with recording of the family history and pedigree charting. History of trauma, occupation, exercise, associated medical disease, and cold paresis were noted. Muscle wasting, power, reflex changes, and tone were recorded. Sense of pinprick, temperature, joint position, and vibration were measured in all patients. Evidence of Horner syndrome, sweating of palms, and postural hypotension were also recorded.

Spinal MRI was performed in all the patients who could afford the procedure. Sagittal and axial sections were performed using T1, T2, and proton density sequence using a 2-T scanner operating at 1.5 T (Magnetome SP, Siemens, Germany). The nerve conduction studies included motor nerve conduction velocity studies of the median, ulnar, and peroneal nerves and sensory nerve conduction studies of the median, ulnar, and sural nerves using a standard technique (Neuromatic 2000; Dan-tec, Skovlund, Denmark). The results of the nerve conduction studies were compared with our laboratory reference ranges, which were determined from 32 healthy adult volunteers.

For the SMN1 and SMN2 gene deletion study, DNA was extracted from peripheral leukocytes of the patients. The presence or absence of exons 7 and 8 of the SMN1 and SMN2 genes was determined by polymerase chain reaction (PCR)—restriction fragment length polymorphism. The PCR for exon 7 (amplified with RHI and mismatch primer X7-Dra or reverse primerb) and exon 8 (amplified with 541C960 and 541C1120 primers) was performed with an initial denaturation at 96°C for 7 minutes followed by 35 cycles (94°C, 62°C, and 72°C for 1 minute each). The PCR products were digested by restriction enzymes DraI and Ddel, respectively, for exons 7 and 8 and separated on 10% polyacrylamide gel electrode visualized in UV and photographed by a documentation and analysis system (Alpha Imager 1220; Alpha Innotech Corporation, San Leandro, Calif).

**RESULTS**

Our results are based on 15 patients from 14 families. In one family, 2 brothers were affected (Figure 1A). There was no family history of similar disease in the remaining families, including 10 first-degree relatives who were personally examined. The age of the patients ranged from 15 to 30 years (mean age, 21 years). The mean duration of symptoms was 2.9 years (range, 1-10 years). All the patients were Hindu except one, who was Muslim. There was no consanguinity, and all the patients were male. Two patients had a history of trauma; one each had head injury (15 years ago) and mild cervical trauma (10 years ago). After the injury, the patients were asymptomatic for several years (range, 7.5-13 years). Two patients had a history of pulmonary tuberculosis, and 1 had hyperhidrosis of the palms. In one patient with a positive family history, the brother developed HD at the age of 17 years; this patient was included in the study group.

The mean age at the time of onset of disease was 18 years (range, 15-23 years). The symptoms started in the right upper limb in 12 patients and the left upper limb in 3. The disease progressed to involve the other side in...
8 patients for a mean duration of 1.4 years (range, 0.5-2.0 years). Cold paresis was present in 6 patients and Horner syndrome in none. Polyminimyoclonus was present in all the patients. Biceps, triceps, and supinator reflexes were present in all, whereas knee and ankle reflexes were brisk in 4 patients. Plantar response was flexor and sensations were normal in all the patients.

The nerve conduction velocity of the median and ulnar nerves was normal in 13 patients. (The median motor nerve conduction in 1 patient and the ulnar motor nerve in 2 were unrecordable.) Median compound muscle action potential was reduced in 7 patients. Sensory conduction velocity, however, was normal. Concentric needle EMG revealed fibrillations in 10 patients, fasciculations in 15 patients, and neurogenic changes in the C7, C8, and T1 myotomes in all patients. The EMG findings were unilateral in 5 and bilateral in 10, and subclinical changes were present in the other upper limb in 2 patients. The EMG findings of other muscles beyond the C7, C8, and T1 myotomes, which started unilaterally but eventually progressed to the other limb in 8 patients. The EMG and nerve conduction velocity findings helped not only in documenting the restricted segmental involvement but also in ruling out a number of other conditions, such as brachial neuritis, multifocal motor block, and mononeuropathy multiplex. From South India, brachial monomelic amyotrophy has been reported. These patients, however, also had wasting of the biceps and deltoid, unlike ours in whom wasting was restricted to the C7, C8, and T1 myotomes. In addition, progression of neurologic deficit was seen for up to 5 years in most patients followed by a stationary phase without any evidence of fresh neurologic deficit, supporting a benign nature of illness. In this study, however, none of the patients had familial occurrence, and MRI or genetic studies were not conducted.

Japanese investigators have suggested that HD may be due to microvascular changes following chronic trauma to the spinal cord during flexion and extension of the neck, especially during adolescence when there is rapid growth.5 In our MRI study, cord atrophy was present in 7 patients and dilated venous plexus in 3, although we did not perform MRI in flexion and extension. Anterior horn cell susceptibility to ischemia might account for the atrophy of the anterior horn cells fol-

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**Table. Clinical Features, Electromyography, and Magnetic Resonance Imaging Findings of Patients With Hirayama Disease**

<table>
<thead>
<tr>
<th>Patient No./ Age, y</th>
<th>Age at Disease Onset, y</th>
<th>Duration of Illness, y</th>
<th>Progression, y</th>
<th>Family History</th>
<th>Wasting</th>
<th>Polyminimyoclonus</th>
<th>Lower Limb Hyperreflexia</th>
<th>Cord Atrophy</th>
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<td>4/16</td>
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Abbreviations: ND, not determined; +, positive; −, negative.

Our study on HD is the first study, to our knowledge, that reports comprehensive evaluation of clinical, neurophysiologic, MRI, and gene deletion analysis. The patients presented with a homogeneous clinical picture characterized by weakness and wasting of the C7, C8, and T1 myotomes, which started unilaterally but eventually progressed to the other limb in 8 patients. The EMG and nerve conduction velocity findings helped not only in documenting the restricted segmental involvement but also in ruling out a number of other conditions, such as brachial neuritis, multifocal motor block, and mononeuropathy multiplex. From South India, brachial monomelic amyotrophy has been reported. These patients, however, also had wasting of the biceps and deltoid, unlike ours in whom wasting was restricted to the C7, C8, and T1 myotomes. In addition, progression of neurologic deficit was seen for up to 5 years in most patients followed by a stationary phase without any evidence of fresh neurologic deficit, supporting a benign nature of illness. In this study, however, none of the patients had familial occurrence, and MRI or genetic studies were not conducted.

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**Figure 2. Absence of the SMN gene deletion in a patient with Hirayama disease.** Exon 7 polymerase chain reaction (PCR)–restriction fragment length polymorphism with Dra I Lanes 1 and 3, patient’s undigested PCR product; lanes 2 and 4, patient’s sample without SMN1 deletion; lane 5, 50–base pair marker.
lowing a microcirculatory disturbance in the anterior spinal artery territory. In such a situation, corticospinal tracts are likely to be affected because of their strategic location in the border zone. Four of our patients had lower limb hyperreflexia, but tone and power were normal in the lower limb muscles. In an earlier study, we evaluated the lower limb hyperreflexia in HD using H reflex studies and concluded that hyperreflexia is not pathologic in view of vibratory inhibition, which is regarded as a specific test of pyramidal dysfunction. Ischemic theory of HD has been disproved in an autopsy study. An alternative hypothesis of HD is a benign focal variant of SMA.

In the present study, both SMN1 and SMN2 gene deletions were found to be negative in all patients. The SMN1 and SMN2 gene deletion study has been advocated for carrier detection, prenatal analysis, and patient diagnosis. Deletion of the SMN1 gene has been reported in 95% of patients with SMA, especially types 1 and 2. Because most of our patients were adults, the likelihood of finding an SMN1 gene deletion was low. Occurrence of HD in the brother of a patient was of interest. A similar family history has been reported in an earlier study, by Hirayama himself, as well as in male twins who developed HD at the same age. The SMN1 and SMN2 gene deletion studies evaluate the centromeric and telomeric SMN gene deletion; the results of these studies were negative in our patients. Presence of the homozygous SMN1 and SMN2 genes in all the patients with HD, occurrence exclusively in male patients, and occasional occurrence in brothers point toward a role of the X chromosome in the genesis of HD, although this needs further evaluation.

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