Original Article

Phenotypic, Electrophysiologic, and Imaging Spectrum of Hirayama Disease from Northern India

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Abstract

Background and Objectives: Cervical flexion-induced myelopathy, also known as Hirayama disease (HD), is a lower motor neuron disorder seen mainly in adolescents and young adults, affecting the C7–T1 myotomes, presenting as asymmetric weakness with wasting of one or both the distal upper limbs. We aimed to describe the clinical features, electrophysiology, and radiologic features of HD in a tertiary care institute in northern India. **Methods:** One hundred and forty patients between 2017 and 2022 with clinical and imaging features consistent with HD were retrospectively reviewed from the All India Institute of Medical Sciences-Comprehensive Neuromuscular Diseases center database. **Results:** Majority were males with the mean age of onset of illness being 17.8 years. The median duration of the symptoms was 3 (1.5–4) years. Sixty-nine (49%) patients had unilateral involvement, and the disease was actively progressing in 88 (63%) patients at presentation. Two families had history of HD in two (1.4%) siblings. Electromyography showed abnormal findings in the clinically involved limb in all the patients and in the clinically uninvolved limb in 17/50 (34%) patients. Flexion magnetic resonance imaging (MRI) demonstrated forward dural displacement in 134 (96%) patients and asymmetric cord flattening in 124 (88.5%) patients. Disability was graded as mild, moderate, and severe; 12 (13%) had severe disability. The majority were managed conservatively, and four underwent surgery for HD. **Conclusion:** A high index of suspicion of HD needs to be kept in a young male presenting with distal upper limb weakness and atrophy. Dynamic MRI of the cervical spine in young adults presenting with hand wasting is inevitable. This disease needs to be managed aggressively and early to prevent serious dysfunction and loss of productivity.

Keywords: Hirayama disease, dynamic MRI, electromyography, cervical collar

Introduction

Keizo Hirayama, a Japanese neurologist, described Hirayama disease (HD) in 1959.[1] HD manifests with unilateral or bilateral asymmetric weakness of the distal upper limbs, and is predominantly a disease of males between 15 and 25 years of age.[1,2] HD occurs as a result of forward dural displacement that occurs during neck flexion, causing impingement of the cervical spinal cord. The disease manifests insidiously and progresses to involve the intrinsic hand and medial forearm muscles supplied by the C7 to T1 myotomes with relative preservation of brachioradialis muscle. The disease usually progresses for a period of about 2–5 years and later plateaus. Treatment involves cervical collar application as well as surgical decompression; both aim to avoid neck flexion.[3] A spectrum of cervical magnetic resonance imaging (MRI) features has been described in HD, which helps in clinching the diagnosis.[4–6] We aimed to describe the clinical features and the electrophysiologic and radiologic profile of 140 HD patients. We aimed to describe the clinical features and the electrophysiologic and radiologic profile of 140 HD patients.

Methods

Patients' data was retrospectively collected from the All India Institute of Medical Sciences-Comprehensive Neuromuscular Diseases center database. The study received approval from the AIIMS institute ethics committee and those recruited in an ongoing International Centre for Genomic Medicine in Neuromuscular Diseases project. Data from patients between January 2017 and December 2022 were collected.

Inclusion criteria

Patients were included if they presented with (a) weakness and wasting of mainly C7–T1 myotomes in one upper limb or both the upper limbs, (b) insidious onset, (c) electromyography (EMG) findings of chronic denervation in

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Submitted: 01-May-2024 **Revised:** 31-Jul-2024 **Accepted:** 03-Aug-2024
Published: 21-Oct-2024

DOI: 10.4103/aian.aian_348_24

the clinically or subclinically involved muscles, (d) no sensory, cranial nerve, bowel, and bladder or cerebellar deficits, and (e) neutral and cervical flexion MRI findings consistent with HD.

Exclusion criteria

(a) History of poliomyelitis in the past
(b) Electric shock injury in the past
(c) Significant spinal injury or trauma to the extremities
(d) History of toxin exposure
(e) Abnormal nerve conduction findings other than reduced or absent compound muscle action potential (CMAP)
(f) Compressive lesions detected by cervical MRI.

The medical records were meticulously reviewed, and the neurologic history, clinical examination findings, and investigations like routine hemogram, renal and liver function tests, and creatine kinase were noted. A telephonic follow-up of the patients was also done in the case of missing history, and to confirm the exclusion criteria and assess the grade of disability. Electroneuromyography data was retrieved from the electrophysiology lab database. In most patients, a needle EMG was performed in the distal and proximal muscles in the affected upper limb (s) and the other uninvolved upper limb. Motor (median, ulnar, tibial, and peroneal) and sensory (upper limb- median and ulnar; lower limb- sural) conduction studies of both the upper limbs and one lower limb were performed. All patients had a cervical spine MRI carried out on 1.5 or 3 T MRI systems in both neutral and neck flexion positions. The MRI findings pointing toward HD diagnosis, like anterior dural displacement, asymmetric cord flattening, cord atrophy, intramedullary cord hyperintensity, epidural flow voids, and enhancement of epidural crescent, were looked for in these patients. Treatment details (conservative management with a neck collar or surgical decompression) were also documented. The disability secondary to the weakness and atrophy was also noted down as mild, moderate, or severe based on a grading scale as follows[7]:

Mild: Motor functions are minimally affected, and the patient can carry on with all activities of daily living and occupation without any help.

Moderate: Motor functions are moderately involved; patient requires assistance to carry out certain activities of daily living.

Severe: Patient is forced to perform motor tasks with the opposite upper limb or is forced to change the occupation.

Statistical analysis

Data were analyzed using the Statistical Package for the Social Sciences Software Version 26.0. Results are displayed as mean ± standard deviation, median (interquartile range), and range for continuous variables and frequency (%) for categorical variables.

Results

A total of 223 patients' medical records were meticulously screened for eligibility, and 83 were excluded [Figure 1]. One-hundred forty patients were recruited between the years 2017 and 2022, who satisfied the study criteria.

Clinical characteristics of the patients

The mean age of patients at presentation was 21.2+4.8 years. Of the patients, 138 (98.6%) were males, with a male to female ratio of 69:1. The youngest was 13 years of age and the eldest was 35 years of age. The mean age of patients at the onset of limb weakness was 17.8 ± 3.4 years. The median duration of symptoms before presentation was 3 (1.5–4) years. All patients presented with upper limb distal amyotrophy without neck or radicular pain. Predominantly, the amyotrophy involved intrinsic hand muscles, the forearm flexors, and the extensors. Eleven (8%) patients were noted to have involvement of the more proximal upper limb muscles like the biceps and deltoid. Sixty-nine patients (49%) had unilateral involvement, while the others (51%) were noted to have bilateral upper limb involvement in an asymmetric fashion. Family history was positive in two cases. Both the families had two brothers each with HD, which was confirmed with their clinical presentation and consistent cervical MRI findings. Blood samples were collected from one family for exome sequencing to test for a possible pathogenic genetic mutation. Figure 2a and b shows the characteristic findings in a 20-year-old male with HD.

Cold-induced worsening, brachioradialis sparing (oblique atrophy), and polyminimyoclonus were observed in 105 (75%), 139 (99%), and 89 (63.5%) patients, respectively. Fasciculations, muscle cramps, and tremors were observed in 100 (71%), 54 (38.5%), and 66 (47%) patients, respectively. The disease was actively progressing in 88 (62.8%) patients at the time of presentation. Tendon reflexes were normal to hypoactive in 120 (86%) patients. Exaggerated reflexes in the upper limb were seen in 20 (14%) patients. Exaggerated knee and ankle jerks were noted in 11 (8%) patients. No patients had Hoffmann's sign, Babinski's response, or clonus. Table 1 summarizes the clinical characteristics of the 140 HD patients.

Electrophysiology findings

Complete electrophysiology data were available in 106 (76%) patients and the details are given in Table 2.

Dynamic cervical MRI characteristics

The salient cervical MRI features on neutral and flexion imaging of a 30-year old male patient with HD are given in Table 3.

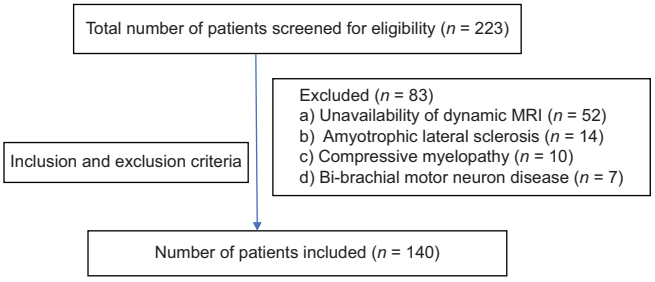

Figure 1: Patient inclusion in the study

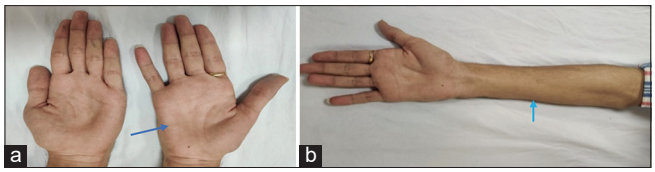

Figure 2: Involvement of muscles in HD. (a) Blue arrow shows amyotrophy of ulnar more than thenar muscles of hand. (b) Blue arrow shows medial forearm wasting with preservation of brachioradialis

Disability

Telephonic follow up of the patients was done to assess disability. Information regarding the same was available in 112 patients; 111 (99%) patients reported some form of disability. Progression of weakness from baseline was reported by 50/88 (57%) patients. Twenty-five patients had completed follow-up of 4 years duration and none reported progression. The grading of disability due to HD is given in Table 4.

Treatment details

Majority of the patients were managed conservatively. Four underwent cervical decompression surgery. Before cervical laminectomy with duraplasty, three patients reported moderate and one patient reported severe disability. Weakness stabilized in all the patients after surgery, and none reported improvement or deterioration of weakness postsurgery after a mean follow up of 2.5 years. Treatment details are elaborated in Table 5.

Discussion and Conclusion

HD manifests as juvenile-onset amyotrophy of upper limbs involving the C7–T1 segments, with preservation of brachioradialis muscle.[3] We describe one of the largest cohorts of MRI-confirmed HD from India over a period of 6 years. The largest descriptive study on monomelic amyotrophy (MMA) till date from India is by Nalini et al.,[7] and they had reported 224 patients of brachial MMA over a period of 35 years. However, this study lacked the dynamic MRI confirmation of HD diagnosis in most patients. Various large cohorts of HD are compared in Supplementary Table 1.

In our study, the mean age of patients at the disease onset was 17.8 years, which is similar to previous reports.[7–11] A striking male preponderance is also seen, with a male to female ratio of 69:1, which is compatible with studies in the past.[7–11] All were younger than 26 years, except one who had an age of onset at 35 years, with an illness duration of 2 years; HD with onset after 30 years of age has been infrequently reported before.[12–14]

Transient limb weakness on cold exposure, called cold paresis, was noted in 105 (75%) patients. This is a very sensitive indicator for HD, as it is not seen in any other anterior horn cell disease. Cold paresis may occur due to autonomic dysfunction or conduction block involving the muscle membrane in reinnervating muscles.[15] Polyminimyoclonus, fasciculations, and cramps were seen in 63.5%, 71%, and 38.5% patients, respectively, similar to previous observations.[7,11] Fasciculations ensue due to damage to the anterior horn cells; repetitive neck flexion leads to cord compression, causing ischemic injury to the anterior horns, culminating in anterior horn cell death.

Table 1: Clinical characteristics

Clinical characteristics	n=140
Mean age at presentation, years	21.2±4.8 (range 13–35)
Male:female	138 (98.6):2 (1.4)
Mean age of symptom onset, years	17.8±3.4
Age of onset (range), years	13–35
Median symptom duration, years	3 (1.5–4)
Progressive distal upper limb weakness with wasting	140 (100)
Polyminimyoclonus	89 (63.5)
Fasciculations	100 (71)
Tremors	66 (47)
Cramps	54 (38.5)
Brachioradialis sparing	139 (99)
Cold-induced worsening	105 (75)
Involvement of biceps and deltoid	11 (7.8)
Unilaterality	69 (49)
Actively progressing disease at presentation	88 (63)
Positive family history	2 (1.4)
Normal to reduced tendon reflexes	120 (86)
Exaggerated upper limb reflexes	20 (14)
Exaggerated lower limb reflexes	11 (8)
Extensor plantar response	0
Clonus	0
Hoffmann's sign	0
Spread of reflexes	0

All the continuous variables are presented as mean± SD or median (IQR). All the categorical variables are presented as number (%)

Table 2: Electrophysiology findings

NCS and EMG findings (at presentation)	n=106
Normal sensory nerve action potential	106 (100)
Reduced CMAP amplitude	
Median	26 (24.5)
Radial	40 (38)
Ulnar	70 (66)
EMG-chronic denervation with motor unit loss MUAPs	106 (100)
Acute denervation (fibrillations and PSW)	87 (82)
Normal motor CMAP amplitude	23 (22)
EMG changes in the uninvolved limb (*n*=54)	18 (33)

All the variables are presented as number (%). CMAP: compound muscle action potential, EMG: electromyography, MUAP: motor unit action potential, NCS: nerve conduction study, PSW: positive sharp waves

Table 3: Dynamic MRI findings

MRI findings	n=140
Anterior dural displacement	134 (96)
Asymmetric anteroposterior cord flattening	124 (88.5)
Atrophy of the cord	111 (79)
Intramedullary cord hyperintensity	73 (52)
Epidural flow voids	100 (71)
Epidural crescent enhancement (*n*=72)	64 (89)

All the variables are presented as number (%). MRI: magnetic resonance imaging

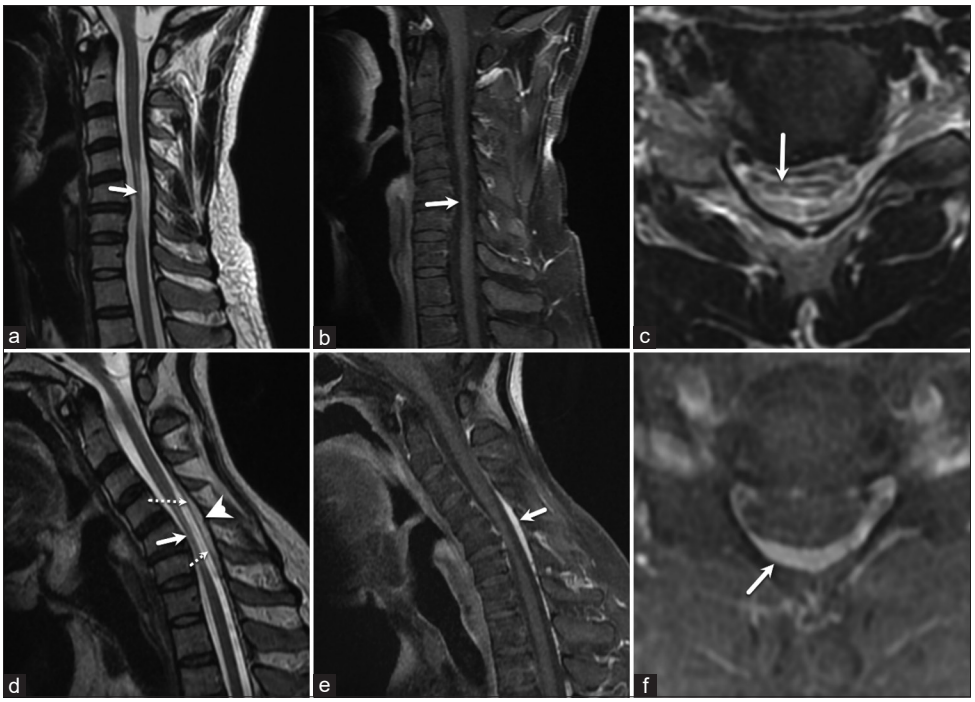

Figure 3: A male patient, aged 30, presents with an asymmetrical wasting of muscles in his hand. Upon examination using a neutral position sagittal T2-weighted MR image (a), it is observed that there is atrophy and hyperintensity (arrow) in the cervical cord at the C4–C6 level. Axial T2-weighted image (c) shows a symmetrical hyperintense signal in the bilateral anterior horn cells, resulting in a distinctive "Snake Eye Appearance" and an asymmetric flattening of the right hemicord (arrow). The post-gadolinium fat-suppressed sagittal T1-weighted MR image (b) reveals no enhancement or widening of the posterior epidural space. In the flexion position, the sagittal T2-weighted MR image (d) demonstrates an anterior displacement of the spinal cord (arrow) and posterior dura (broken arrow), along with a widening of the posterior epidural space (arrowhead) and hyperintense signal in the spinal cord. The post-gadolinium fat-suppressed sagittal (e) and axial (f) T1-weighted flexion MR images reveal the enhancement of an epidural venous plexus (indicated by arrows) extending from the C4 to C7 vertebral levels. MR: magnetic resonance

Table 4: Disability grading

Disability grade at presentation	n=111
Mild	59 (53)
Moderate	38 (34)
Severe	14 (13)

All the variables are presented as number (%)

Table 5: Treatment of HD

Treatment modalities	n=140
Physiotherapy	121 (86)
Cervical collar + physiotherapy	102 (73)
Surgery	4 (2.85)

All the variables are presented as number (%). HD: Hirayama disease

Most patients in this cohort showed reduced to normal tendon reflexes; a small proportion had hyperreflexia – upper limb in 14% and lower limb in 8% of patients. Hoffmann's sign, extensor plantar response, spread of reflexes, and clonus were distinctively absent. Thus, exaggerated tendon jerks was the only evidence of upper motor neuron (UMN) involvement in our series. In the study by Peiris et al.,[16] the upper limb reflexes were noted to be absent or reduced. In the study by Hirayama,[2] the upper limb reflexes were hypoactive to normal, and 40% of 20 patients had lower limb hyperreflexia. Earlier reports showed a similar finding of increased deep tendon reflexes in a few cases in the lower limbs.[2,17–19]

Our study had two families consisting of two siblings each with HD. The other cohorts with familial HD are given in Supplementary Table 2. Two variant genes have been identified, *KIAA1377* (also known as Centrosomal Protein 126 [CEP 126]) and *C5orf42,* in four Korean males with MMA, and the possible association with HD needs further research.[20]

Nerve conduction studies showed reduction of ulnar CMAP amplitude more than median CMAP amplitude. This finding is consistent with the more severe atrophy on the ulnar side; this is known as the reverse split hand phenomenon as opposed to Amyotrophic lateral sclerosis (ALS), where there is predominantly atrophy of the median compared to the ulnar innervated hand muscles.[21] Needle EMG demonstrated denervation changes predominantly in the C7–T1 myotomes, with proximal spread to the C5 and C6 myotomes in 7.8% of cases. Proximal involvement is not uncommon in HD; it has been noted in most previous studies, ranging from 2% to 22%.[8,9,11,22] Uninvolved upper limb demonstrated EMG changes in 33% of the cases, which is similar to earlier observations.[22] A few studies in the past have also noted neurogenic motor unit potentials in the lower limb, sternomastoid, thoracic, and paravertebral muscles. The

concept of HD being a benign entity with restricted C7–T1 myotomal involvement is going away now.[23]

Dynamic MRI revealed anterior dural displacement in 134 (96%) cases, similar to the observations made by Hirayama[2] (87% of 47) and Huang[10] (95% of 40) [Figure 3]. Anterior dural displacement was first described by Pradhan and Gupta[19] in 1997 and reiterated by Hirayama[1] in 2000. This finding is usually encountered in the progressive phase of the illness, and it has a sensitivity and specificity of 93% and 98%, respectively, in diagnosing HD.[5] A dynamic cervical MRI has a sensitivity and specificity of 71% and 100%, respectively, for making a diagnosis of HD.[24]

Asymmetric anteroposterior cord flattening was noted in 88.5% of patients in this cohort. This is another important finding which is encountered in progressive disease phase and has been reported in previous studies, albeit with a reduced frequency.[4,25] Localized cervical cord atrophy was encountered in 79% patients; this is attributed to the anterior horn cell ischemic changes leading to necrosis. Epidural flow voids were noted in 71% and enhancement of epidural crescent in 89% (64/72) patients. Ciceri et al.[26] postulated that venous congestion during cervical flexion might contribute to cord ischemia. On flexing the neck, venous drainage toward the jugular veins decreases, with an increased flow to the posterior internal vertebral plexus. This ensues due to the negative pressure in the posterior epidural space as a result of anterior dural displacement. Various surgical approaches in HD aim to reduce the dural shift and thereby prevent the epidural venous congestion contributing to cord ischemia.

Most patients were managed with the help of cervical collar and physiotherapy. Collar therapy protects the cervical motor neurons from the damage during neck flexion and leads to disease stabilization.[27] Even though it is the first-line treatment, a recent clinician-led consensus statement recommended surgery in those with protracted disease, intolerance to collar, or occurrence of pyramidal signs.[28] Four patients underwent cervical laminectomy with duraplasty in this cohort as they had ongoing progression of weakness with wasting despite using collar. All of them had moderate to severe disability at presentation. The weakness stabilized in all after a median follow-up of 4 years. Even though there is some evidence from observational studies regarding possible efficacy of surgery in HD, there are no clear-cut guidelines on the optimal surgical procedure.[29–32] Randomized controlled trials on the collar versus surgical approach are merited, as well as those on anterior versus posterior neck surgical approaches. There is persisting uncertainty on the benefits of surgery versus hard collar application in HD; while surgery may not completely cure the problem, it will avoid the need to use hard cervical collars, which are not usually palatable or practical.

We recognize certain limitations in our study: the retrospective design and the nonavailability of electrophysiology data in a few patients. We also acknowledge that we could not perform handheld dynamometry and calculate the Jebsen–Taylor scores as data were collected retrospectively. Genetic studies in these patients are ongoing and will be reported in a separate paper. However, this study is the largest till date on HD from northern India, which has comprehensively described the clinical, imaging, and electrophysiologic profile of HD.

A high index of suspicion of HD needs to be kept in a young male presenting with distal upper limb weakness and atrophy. Dynamic MRI of the cervical spine in young adults presenting with hand wasting is inevitable. This disease needs to be managed aggressively and early to prevent serious dysfunction and loss of productivity. More studies are needed to throw light on the etiopathogenesis and address the geographic preponderance of HD. Good quality, head-to-head randomized controlled trials on conservative versus surgical management of HD need to be performed in future.

Author contributions

WLM, MGH, and RDSP received funding from The Lily Foundation, and WLM and RDSP received funding from a seedcorn award from the Rosetrees Trust and Stoneygate Foundation. RDSP is supported by a Medical Research Council (UK) Clinician Scientist Fellowship (MR/S002065/1), MGH and RDSP are supported by the Medical Research Council (UK) award MC_PC_21046 to establish a National Mouse Genetics Network Mitochondria Cluster (MitoCluster), and WLM, MGH, VVY, MVP, TA, RB, and RDSP are supported by the Medical Research Council (UK) strategic award MR/S005021/1 to establish an International Centre for Genomic Medicine in Neuromuscular Diseases (ICGNMD).

Financial support and sponsorship

This work was supported by a Medical Research Council strategic award to establish an ICGNMD MR/S005021/1 (Dr. Vishnu VY).

Conflicts of interest

There are no conflicts of interest.

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Supplementary Table 1: National and International series on Hirayama disease

Characteristics	Sobue, et al. 1978 (Japan)[3]	Peiris, et al. 1989 (Srilanka)[4]	Tashiro, et al. 2006 (Japan)[5]	Zhou, et al. 2010 (China)[6]	Nalini, et al. 2014 (Southern India)[1]	Gourie Devi, et al. 2003[7]	Huang, et al. 2008 (Taiwan)[8]	Samanta, et al. 2022 (Eastern India)[9]	Present study, 2023 (Northern India)
Type of study	Prospective observational	Prospective observational	Nationwide registry	Retrospective	Retrospective	Prospective observational	Retrospective	Prospective observational	Retrospective
Study duration, years	21	15	2	NA	35	NA	10	4	6
No. of patients (%)	71	102	333	192	224	44	40	128	140
Male:Female	5:1	10:1	8:1	7:1	10:1	10:1	7:1	34:1	69:1
Mean age at presentation, years	NA	20	18.4	16.8	23.5	19.8	16.8	21.7	21.2
Mean illness duration, years	NA	NA	NA	4.74	3.9	4.1	NA	3.2	3 (1.5-4)*
Hand muscle wasting, n (%)	71 (100)	102 (100)	296 (89)	192 (100)	224 (100)	43 (97.7)	40 (100)	116 (91)	140 (100)
Forearm wasting, n (%)	7 (100)	NA	251 (75)	192 (100)	100 (44.6)	24 (54.5)	NA	NA	140 (100)
Brachioradialis sparing, n (%)	71 (100)	NA	228 (68)	96 (50)	130 (63.1)	NA	NA	NA	139 (99)
Proximal UL involvement, n (%)	11 (15)	1 (0.98)	74 (22)	33 (17)	8 (3.6)	1 (2.3)	8 (20)	10 (7)	11 (7.8)
Unilateral involvement, n (%)	47 (66)	39 (38)	240 (72)	167 (87)	194 (87)	38 (86)	24 (60)	90 (73)	69 (49)
Bilateral involvement, n (%)	24 (34)	63 (62)	93 (28)	25 (13)	30 (13)	6 (14)	16 (40)	26 (18.5)	71 (51)
Family history, n (%)	1 (1.4)	0	2 (0.6)	1 (0.52)	0	0	0	4 (2.8)	2 (1.4)
UMN involvement, n (%)	10 (14)	NA	7 (2.1)	12 (6.3)	41 (18)	4 (9.1)	0	8 (5.7)	20 (14)
EPS data, n (%)	56/73 (77)	102 (100)	265 (79.5)	192 (100)	200 (89)	44 (100)	37 (92.5)	128 (100)	106 (76)
Dynamic MRI, n (%)	NA	0	229 (69)	127/176 (72)	20 (8.9)	NA	38 (95)	128 (100)	140 (100)
Surgical management, n (%)	0	NA	41 (12.3)	5 (2.6)	NA	NA	NA	NA	4 (2.85)

*median. UMN: Upper motor neuron, EPS: Electrophysiologic studies, MRI: Magnetic Resonance Imaging

Supplementary Table 2: Familial reports of HD

Case series and reports of HD	Positive family history (n)
Our study (2022)	2 families
Nalini, et al. (2009, 2017)[19,20]	6 families
Tashiro, et al. (2006)[5]	2 families
Misra, et al (2005)[21]	2 families
Zhou, et al (2010)[6]	1 family
Sobue, et al (1978)[3]	1 family
Samanta, et al (2022)[9]	4 families
Valerio, et al (2016)[22]	1 family
Panday, et al (2016)[23]	1 family