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THIRUVANANTHAPURAM, KERALA



“CLINICO RADIOLOGICAL AND ELECTROPHYSIOLOGICAL PROFILE OF PATIENTS WITH HIRAYAMA DISEASE- A RETROSPECTIVE STUDY”

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By

Dr. Karthika Ajit V

Postdoctoral fellow, Neuromuscular disorders

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Department of Neurology

Sree Chitra Tirunal Institute for Medical Sciences and Technology

Thiruvananthapuram

DECLARATION BY THE STUDENT

I, Dr. Karthika Ajit V, hereby certify that I had personally carried out the work depicted in the thesis titled, **“Clinico radiological and electrophysiological profile of patients with Hirayama disease -A retrospective study”**. No part of this thesis has been submitted for the award of any other degree or diploma prior to this date.



Date: 29-11-2023

Dr. Karthika Ajit V

CERTIFICATE BY THE RESEARCH GUIDE

Name of the Guide: Dr. Sruthi. S. Nair

Division/Department: Department of Neurology

This is to certify that Dr. Karthika Ajit V, Department of Neurology of this institute has fulfilled the requirements prescribed for the Postdoctoral fellow in Neuromuscular disorders of the Sree Chitra Tirunal Institute for Medical Sciences and Technology, Trivandrum. The thesis entitled, **‘Clinico radiological and electrophysiological profile of patients with Hirayama disease -A retrospective study’** was carried out under my direct supervision. No part of the thesis was submitted for the award of any degree or diploma prior to this date. Clearance was obtained from the Institutional Ethics Committee for carrying out the study.



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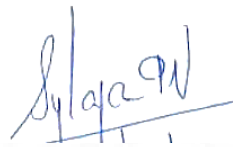
Dr. Sruthi.S.Nair

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Thiruvananthapuram

29 -11- 2023



Dr. Sylaja P.N

Professor and Head

Department of Neurology

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INTRODUCTION

INTRODUCTION

Hirayama disease (HD) is characterised by the juvenile onset of unilateral or asymmetric weakness and amyotrophy of the hand and ulnar forearm with sparing of brachioradialis muscles and no objective sensory or lower limb involvement (1). It is most commonly seen in Asian males. The first case was reported in 1959 by Keizo Hirayama (1). By 1972 a total of eight cases were reported (2). Similar cases were reported from India during the 1980s and 1990s (3). The first autopsy case was performed in Japan in 1982 wherein the spinal cord showed anteroposterior flattening and ischemic necrotic changes of the anterior horn cells of cervical cord from C5 -T1 was noted, with C7 and C8 being most severely affected (4).

The disease presents in the late adolescence with sporadic occurrence and almost only males are affected (5). Familial forms rarely occur (6,7). The typical clinical manifestations include insidious onset of distal weakness and wasting, predominantly on the ulnar side, in one upper extremity or asymmetrically in both upper extremities with initial progression for 3–5 years, followed by arrest of the disease or a relatively benign period (5). Irregular, coarse tremors in the fingers of the affected hand with mild transient worsening of symptoms when the individual is exposed to a cold environment with the absence of objective sensory loss are the key features. Atypical forms have also been described which include the proximal upper limb involvement, presence of pyramidal signs, sensory deficits and longer disease progression (5,8). The disease causes moderate to severe disability for the patient.

The current implicated hypothesis with regard to pathogenesis of HD is chronic ischemia with compressive injury of the cervical motor neurons caused by neck flexion, which is caused by abnormal forward-shifting of the lower cervical posterior dura on neck flexion (9,10). Neck flexion magnetic resonance imaging (MRI) studies with contrast form an important cornerstone in the diagnosis of HD (11,12). The observed radiologic abnormalities are forward displacement of the posterior wall of the cervical dural sac, cord flattening, atrophy, and the presence of a crescent-shaped high-intensity mass. Conventional electrophysiological studies like nerve conduction study findings of decreased ulnar/median compound muscle action potential (CMAP) ratio and electromyography (EMG) have aided in diagnosing HD (13).

Studies with regard to clinic-radiological and electrophysiological profile has been limited

despite the disease being common and disabling for the young productive adult male population. The assessment of the profile of the patient aids in identification of atypical presentation apart from the common clinical, radiologic and electrophysiological manifestations.





REVIEW OF LITERATURE

REVIEW OF LITERATURE

Hirayama disease, also referred to as juvenile muscular atrophy, characterised by weakness and wasting of distal upper limbs was first reported in 1959 by Keizo Hirayama. (4). It is more common among the Asian males and the onset of symptoms commence in the teens to early twenties. Weakness is either unilateral or asymmetric associated with wasting of hand and forearm muscles supplied by C7-T1 myotomes, with sparing of brachioradialis muscles. There is no sensory involvement.

Since its initial description by Hirayama et al. in 1959, HD has been assigned a number of titles based on how it manifests clinically. There are around 14 different names describing this entity. The term “Brachial MonoMelic Amyotrophy” (MMA) refers to unilateral and distal amyotrophy of a single upper limb, which may spread to the contralateral upper limb in about 20% of cases which was the initially described form (3). Atypical variants such as symmetric amyotrophy of the distal upper limbs and monomelic amyotrophy of the proximal upper limb muscles have also been reported. (14,15). Distal bimelic amyotrophy involving symmetrical amyotrophy of the distal upper extremities with rapid progression to severe motor disability sharing similar MRI features of HD was described by Preetish et al (16). Proximal bimelic amyotrophy or proximo-distal bimelic amyotrophy were considered as variants of the same disease with involvement of higher or lower cervical segments (17). Yavuz et al has condensed the various terminologies and synthesized the disease entity as a type of juvenile muscular atrophy of the upper extremity with proximal, distal, and proximodistal involvement due to radiologically proven and arrested flexion myelopathy without sensory disturbance or with minimal sensory disturbance (18). Nosological classification of this disease is summarised in Table 1.

Nosological classification of this disease is summarised in Table 2.1.

Table 2.1- Nosology of Hirayama Disease

Eponyms	Clinical Presentation
Juvenile muscular atrophy of the unilateral upper extremity	Hirayama et al. in 1959 described the unilateral juvenile amyotrophy of the distal upper-limb
Juvenile nonprogressive monomelic amyotrophy (JNPMA)	Hashimoto in 1972 coined the term JNPMA because of the unilateral and nonprogressive amyotrophy of the upper limb.
Monomelic amyotrophy (MMA)	As the amyotrophy may involve the upper or lower limb, Gourie-Devi et al. in 1984 labelled the term MMA.
Juvenile muscular atrophy of the distal upper extremity (JMADUE)	Biondi et al. in 1989 coined the term JMADUE because of the amyotrophy involved only in the distal upper limb (19)
Juvenile asymmetric segmental spinal muscular atrophy (JASSMA)	Pradhan and Gupta et al in 1997 labelled the term JASSMA because of the bilateral and asymmetric amyotrophy of the upper limbs
Brachial monomelic amyotrophy (BMMA)	Gourie Devi and Nalini et al in 2003 labelled the term BMMA, which represents a case of HD, distinguishing it from crural MMA.
Distal bimelic amyotrophy	Symmetrical amyotrophy of both upper limb distal muscles
Proximal bimelic amyotrophy (PBMA) or proximo-distal bimelic amyotrophy (PDMA)	PBMA is characterized by the bilateral amyotrophy of the shoulder girdles and arms; PDMA affects bilaterally both proximal and distal muscles of the upper limb

Epidemiology

The first ever report of HD was that of 12 cases by Dr. Keizo Hirayama in 1959 who described it as juvenile muscular atrophy of the unilateral upper extremity. Hirayama distinguished this disease from previously known degenerative and progressive motor neuron diseases. The first and the only complete epidemiological survey is from Japan, wherein a nation-wide survey of patients with HD was conducted with majority of patients being males (20). Most of the cases were initially reported from Asia, including Japan (1,2,20,21) Sri Lanka (23), Korea (23), Hong Kong (24) and Taiwan (25). The very first case report from India was by GourieDevi et al in 1984 (3). More cases have been reported from various parts of India thereafter, a larger proportion being from South India (26 -29). Studies conducted from western countries show increasing number of cases including North America, Europe, and Australia (30- 33).

Most of the studies have shown that this disease affects predominantly the male gender. Only very few case reports of female patients with HD have been described (34 -38). In studies of HD, the reported male-to-female ratio exhibited wide variability, ranging across 8.3:1 (281 males to 34 females) and 20:1 in Japan; 2.8:1 in India; and 11:1 (67 males to 6 females) and 31.6:1 (348 males to 11 females) in China (5,20,21,39,40). The age of symptom onset in different studies vary from late teens to early 30s.

Pathogenesis

Initial considerations regarding the etiopathogenesis of HD included viral infections, vascular insufficiency of the spinal cord, heavy physical activity and focal cord atrophy as a result of stretching of neck during neck flexion (25, 41,42). Newer theories including immunological and genetic factors have been proposed over the recent years. (5).

The possible pathophysiologic mechanisms include:

- Dysplasia of the dural sac

Due to the growth spurt that occurs during adolescence, the spinal cord and spinal canal may have disproportionate lengths, which could result in dural sac dysplasia. (43 - 45). This contributes to the tightness of the dura and hence

cervical flexion results in anterior dural displacement and compression of anterior spinal artery causing ischemia if anterior horn cells.

- Nerve root dysplasia

The short length of the cervical roots have been thought to be related to nerve root dysplasia. Neck flexion causes the cord to be drawn anteriorly to the affected side as the dorsal roots are unable to extend (46).

- Abnormalities of the spinal ligament

Loss of elastic fibres of the epidural ligament predisposes to the tightness of posterior duramater. Asymmetric atrophy has been postulated to be due to the asymmetry of the epidural ligaments (47,48).

- Venous dysplasia

Engorged venous plexus that occurs either as a result of negative pressure in the posterior epidural space because of the anterior displacement of the dura, impaired venous drainage in the jugular veins with subsequent venous flow diverted to the posterior epidural plexus or the diversion of blood to the posterior epidural compartment from the compressed anterior venous system (49).

- Ischemic injury to the anterior horn cells of the cervical cord

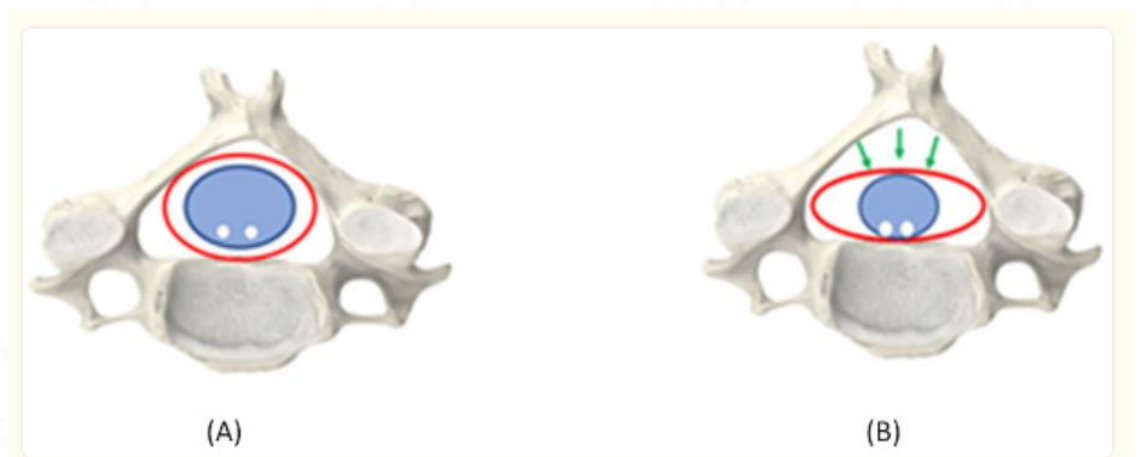
The most widely hypothesised mechanism involved in the pathogenesis of HD is the ischemic injury of the cervical anterior horn and/or nerve root caused by excessive forward displacement of the posterior dura during neck flexion. This has been largely supported by both autopsies and neuropathologic studies done in patients with HD

The theory put forth by Kikuchi et al. that cervical myelopathy is caused by neck flexion is the most frequently accepted of these views (50). In healthy

people, the dura mater around the spinal nerves is anatomically strongly linked to the dorsal periosteum throughout the vertebral canal, however in Hirayama patients, the dura mater is loosely attached to the posterior longitudinal ligament within the spinal canal. The cervical spinal column can stretch by about 3 cm during cervical flexion, and the loose dura mater is unable to adjust to this substantial length change. In individuals with Hirayama disease, the dura mater is thought to stay relatively short and stiff in comparison to the spinal canal and is unable to compensate for the lengthening of the canal.

Due to the anterior displacement of the posterior dura mater during neck flexion, the spinal cord is exposed to compression between the vertebral corpuscles and dura mater. The anterior section of the spinal cord and the blood vessels that supply the anterior horn are exposed to compression as a result of frequent neck flexions, which can lead to ischemia attacks and eventually chronic trauma to the anterior horn. Due to anterior horn compression and ischemia in the afflicted segment, associated muscles experience denervation and atrophy.

Figure 2.1—Anterior horn cell compression during spinal cord flexion



A-Neutral position

B- Arrows show forward shifting of posterior duramater on flexion and compression of anterior horn

- Immunologic factors

High frequency of coexistent atopic disorders, hyperIgEaemia, together with a family history of allergic disorders was reported by Kira et al (51). Another study showed that there could be a link between IgE levels and the duration of disease progression (52). Petrova et al observed that IgA deficiency may have a propensity to contribute to ischemia of the spinal cord in HD patients (53). There is currently no strong evidence that links immunological factors as a causative factor.

- Dynamic instability

Khadilkar et al observed that neck length was more in HD patient in comparison to normal patients (54). Imbalance between the strength of neck flexors and extensors during neck flexion, contributing to dynamic instability, as a risk factor was observed by Li et al (55). In recently published study by Wang et al neutral and flexion Cobb angles in HD patients increased at C6, C7 segments leading to dynamic instability (56).

Genetics and HD

Lim et al. found two variant genes, KIAA1377 and C5orf42, to be associated with HD (57). The two genes were identified by whole-exome sequencing: KIAA1377 (also known as Centrosomal Protein 126 [CEP 126]) and chromosome 5 open reading frame 42 (C5orf42).43 These two genes were identified in four Korean male patients with monomelic amyotrophy, and then by selective genotyping of candidate variants in 24 patients. Further functional studies are required for validation of these results

Familial cases in HD

HD is largely a sporadic condition but there have been reports of HD with a positive family history. In the study cohort of Misra et al, the author observed two brothers with monomelic amyotrophy (58). Nalini et al observed the disease condition in mother and son with age of

onset being the same and the disease progression to bimelic distal amyotrophy noted in the mother (59,60). In other cases, Pandey and Jain reported a father and daughter with bilateral HD, and Sobue et al. reported an affected father and a son (6, 61). Schlegel et al. described a Caucasian father and son with HD like presentation characterized as focal amyotrophy of the upper limb, with onset at the age of 16 in both, suggesting autosomal dominant inheritance (62). Additionally, Hirayama noted incidences of HD in families (2). An autosomal dominant mode of inheritance was suggested by a case series that included a Greek family with four members over three generations and distal limb amyotrophy compatible with HD (63).

Natural history

The natural history of the disease is largely derived from long term follow up studies from Asia. From these studies HD is known to progress, reach a nadir and stabilise after a period of 2- 5 years. Earlier reported cases of HD mentioned the disease progression over two to four years (1,64,65). In one of the largest studies with 279 patients with monomelic amyotrophy, Nalini et al observed the period of progression of motor deficits before achieving stabilisation ranged from one to four years (66). The study observed that a longer period of progression did not alter the prognosis. Most of them had a favourable outcome with good functional capacity. Tashiro et al made an interesting observation that the disease progression ranged between three to six years and was arrested before 25 years of age in majority of patients in his study (20).

Clinical Profile

Typical clinical manifestations

Clinicians have consistently improved their knowledge of HD's clinical symptoms since the disease was originally diagnosed. The compilation of the common clinical manifestations of HD, which consists of five basic symptoms and manifestations, has been made possible, especially in the last ten years, by the continual increase in clinicians' understanding of the disease and the numerous pertinent studies

- (1) Asymmetrical distal weakness and wasting in one or both upper extremities, primarily on the ulnar side. The "reverse split hand syndrome," which is seen more in HD patients has

- severe ulnar side muscular atrophy, and distinguishes the disease from ALS. The hypothenar muscles' innervating AHCs are most vulnerable to this kind of harm. (67)
- (2) Insidious onset with initial progression for 3–5 years, followed by arrest of the disease (1).
 - (3) Irregular, coarse tremors in the fingers of the affected hand(s)
 - (4) Cold paresis which is the mild transient worsening of symptoms when the individual is exposed to a cold environment. It was postulated that cooling resulted in decreased sodium-potassium adenosine triphosphatase activity, leading to transient depolarization due to the inactivation of the electrogenic sodium pump (68).
 - (5) Absence of objective sensory loss

Atypical clinical manifestations

Not all patients with Hirayama disease have the typical symptoms. There are case reports with atypical manifestations like upper motor neuron signs, proximal muscle involvement, rapid progression and subtle sensory deficits.

Pyramidal signs

Pyramidal signs like hyperreflexia and inverted reflex reflect severe cord involvement. In Japan and China, patients with HD were found to have pyramidal symptoms in 2.4% and 10.6% of cases, respectively (69). Additionally, 18.0% and 12.0% of the patients reported by Hassan et al. and Sonwalkar et al., respectively, had upper motor neurone involvement. Upper motor neurone symptoms suggest serious cord involvement and predict a worse result (70,71).

Atrophy of proximal muscles of the upper extremity

The lower cervical spinal cord, particularly the C7-T1 level, is the typical area of the spinal cord that experiences compression in HD. Preethish-Kumar et al. shown that cervical flexion can cause the myelopathies distal, proximal, and proximodistal bimelic amyotrophy (16,17). In addition, Hirayama et al. documented two cases (out of 20) with proximal involvement, one

in which there was weakness in the pectorals and triceps (72). As a result, proximal forms' functional outcomes are probably worse and less definite than those of distal forms.

Long progression

The majority of HD patients experience self-limited illness, achieving stabilisation over a period of 5 years. However, there have been instances when the disease has advanced over more than ten years and the patient's state has slow progression of the disease. The abnormalities seen on imaging do not become better as the condition worsens, suggesting that HD may not always be a self-limiting disease (73).

Sensory deficit

Some HD patients may experience sensory abnormalities because of sensory tract involvement brought on by compressive myelopathy. 19.2% of patients, according to Tashiro et al., had sensory impairment (20).

Imaging manifestations

The most crucial diagnostic device used to assess a patient suspected of having HD is an MRI of the cervical spine in neutral and in flexion (74). The term "dynamic MRI" refers to this kind of imaging. On a 1.5 T or 3.0 T scanner, the image acquisition is carried out while the patient is supine. The scanning involves the following sequences: sagittal and axial T1-weighted sections, sagittal and axial T2-weighted sections, and sagittal and axial T1-weighted images with fat saturation with contrast

(A)Neutral magnetic resonance imaging of the cervical spine

The typical findings on neutral scans include loss of normal cervical lordosis or abnormal curvature of the spine, loss of posterior attachment of dura to the subjacent lamina, localized lower cervical cord atrophy, asymmetric flattening of cord anteroposteriorly, and intramedullary T2 cord hyperintensity (Figure 3A–D). The sensitivity and specificity of findings on neutral cervical spine imaging have been demonstrated by Chen and colleagues (74). Cord thinning, cord flattening, and loss of dural attachment (LOA) to the lamina were

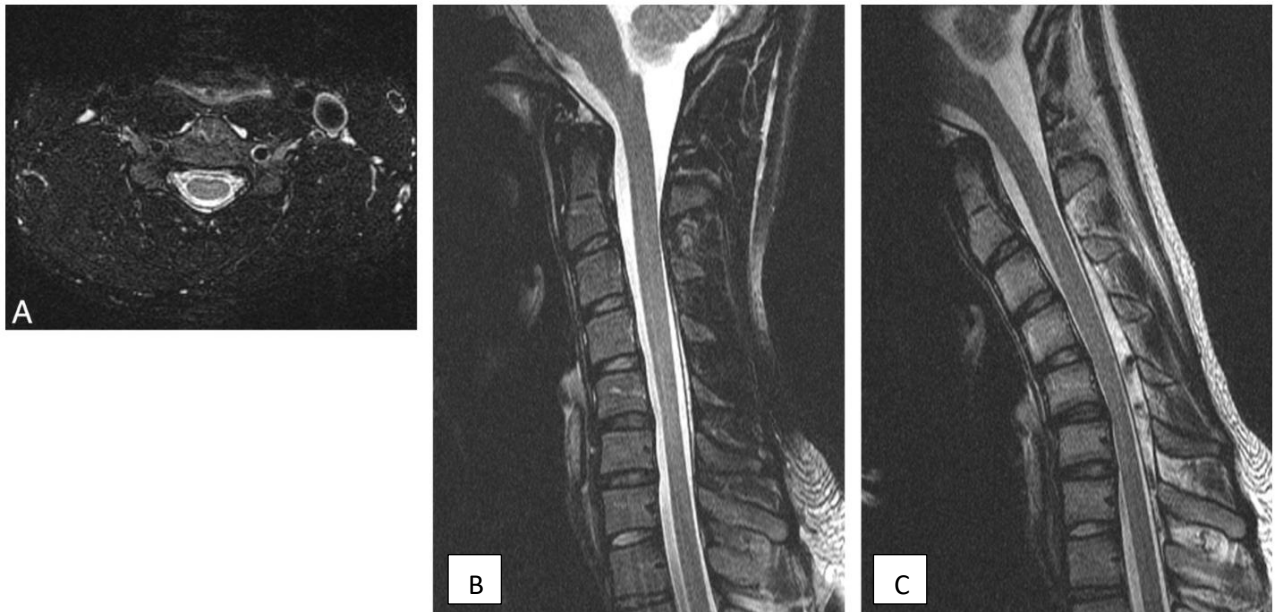
discovered to have more than 80% accuracy in detecting illness among the MRI findings (75). The neutral MRI's most valuable finding was the LOA sign, which had a sensitivity and specificity of 94.0% and 98.0%, respectively (75). An asymmetrical bilateral T2 hyperintense signal, known as the "snake-eye," may be seen in some individuals on axial sections which may indicate poor prognosis heralding the requirement of surgical intervention (76).

Although the majority of the available research points to the necessity of flexion MR imaging in the diagnosis of HD, neutral MR imaging itself was highly specific with reasonably high sensitivity, according to Lehman et al (12). With a prevalence of 93% in their study population, Chen et al identified "loss of attachment" from the posterior dural sac and subjacent lamina as the most significant finding in the diagnosis of HD (74). However, Lai et al. found that without spinal cord compression, up to 46% of patients also had forward movement of the posterior dural sac in healthy people (75).

(B) Flexion MRI of the cervical spine

The most crucial test is a cervical flexion MRI because it reliably establishes the diagnosis in every suspected HD patient. For a sufficient scan, the neck must be flexed at an angle of 35° (9). The important radiologic findings include a high-intensity crescent-shaped mass, epidural flow gaps, asymmetric lower cervical cord flattening, forward displacement of the posterior dura, and cord atrophy (Figure 2.2). The anterior cord displacement is yet another critical symptom that can be noticed. Dural sac tightness on cervical flexion is caused by an imbalance in the formation of the dura sacs along the vertebral canals, which are only connected at the C2-C3 and coccyx. During neck flexion, this causes the dura and the spinal cord to move forward. Additionally, repeated neck flexion results in long-term microcirculatory alterations. In a cohort study, dynamic MRI was noted to have a sensitivity of 71% and specificity of 100% in diagnosing HD (74). Post gadolinium flexion MR images demonstrate moderate-to-intense enhancement in the engorged posterior epidural venous plexus, forming a crescent-shaped epidural mass, which exerts a compression effect over the cord with or without flow voids (11,33). Gupta et al. suggested using 3D-CISS for improved MR imaging visualization of the epidural flow voids (77).

Figure 2.2 – MRI cervical spine findings in Hirayama disease



A- Axial T2W image showing loss of attachment at C5, B- Neutral position MRI shows loss of cervical lordosis with mild atrophy at C5 C6, C- Flexion MRI shows anterior dural shift with near complete obliteration of subarachnoid space, prominent epidural flow voids at C5, C6

Functional imaging

The principle of Brownian motion of water particles is used in diffusion tensor imaging (DTI), which is used in HD diagnosis. Potential indicators include a decreased fractional anisotropy and an elevated apparent diffusion coefficient. The level at which surgery must be conducted can be determined by DTI in addition to evaluating the cord injury. In a study of 10 HD patients, the corticospinal tract DTI abnormalities in the brain were described, and an attempt was made to link them with the clinical results (78). Future research should take functional imaging into account. In 17 patients with HD who had cervical decompression with fusion surgery, functional MRI using the blood oxygen level-dependent approach was investigated (79). A total of 60 patients were scanned both before and after surgery at various time intervals (80). The study revealed ipsilateral motor cortex activation when the affected hand was used compared with the unaffected hand. The activation was reduced following surgical fixation.

Electrophysiology of HD

Electrophysiologic studies play an important role in the diagnosis and exclusion of various HD mimics, primarily amyotrophic lateral sclerosis and cervical spondylotic myelopathy. (13). Motor conduction studies show reduced or normal compound muscle action potential amplitudes with normal distal latencies and conduction velocities (82). The ulnar/median CMAP ratio can be employed in differentiating HD from amyotrophic lateral sclerosis(ALS) and cervical spondylotic myelopathy. The ulnar median CMAP ratio is decreased in patients with HD, higher in patients with ALS, and normal in patients with spondylosis (13). Sensory conduction is normal in patients with HD.

The EMG involving the C7–T1 myotomes include fibrillations and positive sharp waves in those with on-going denervation, and large amplitude, long duration, polyphasic, motor unit action potentials with moderate to discrete recruitment in patients with long-standing disease (83). Spontaneous potentials in EMG shows ongoing disease activity. More than often, denervation and reinnervation potentials are detected in the unaffected limb (82). In atypical cases, proximal involvement of the cervical segments are also observed.

F wave studies usually show normal latencies but results from various studies have shown mixed results. Hassan et al observed F wave conduction velocities to be normal in HD patients (70). In study done by Zheng et al, F wave latencies were prolonged and there was an increase in the number of repeater F waves (84). This finding was postulated to be the result of reinnervation by a distal or proximal axonal sprouting. Moreover, higher average peak to peak amplitude of F waves expressed as a percentage of maximal M wave amplitude was observed on the symptomatic side during neck flexion when compared to neutral posture (84). Other HD mimics like cervical spondylotic myelopathy have delayed F wave latency and lower persistence and normal or lower persistence in motor neuron disease (69).

Evoked potentials have been studied in HD patients which yielded varied results. Latency of somatosensory evoked potential was observed to be normal by Abraham et al whereas N13-

N20 interpeak latency during neck flexion was noted by Park et al (85,86). Motor evoked potential amplitude was decreased, longer central motor conduction time and delayed latency was found in HD patients along with significant reduction in the upper limb amplitude of motor evoked potentials on cervical flexion compared to neutral position (87).

Though the conventional electrophysiological studies like nerve conduction study findings of decreased ulnar /median CMAP ratio and EMG may have aided in diagnosing HD, they may not help in assessing the severity and progression of the disease. This can be achieved by quantitative electrophysiologic methods like motor unit number estimation (MUNE) or motor unit number index (MUNIX) estimation (88,89). Zheng C et al study evaluated MUNE estimation and observed that the MUNE values were significantly lower in all tested muscles in the HD group (88). The same author had evaluated the role of MUNIX in HD with proximal muscle involvement (89). MUNIX evaluation at different time points maybe used as a quantitative indicator in assessing the severity and progression of the disease.

Diagnostic criteria of HD

The new Huashan diagnostic criteria takes into account clinical manifestations, medical imaging manifestations, and electrophysiological examinations, based on recent reports.

Table 2.2 - The Huashan diagnostic criteria for Hirayama disease (40)

	Clinical manifestation	Imaging	Electrophysiology
Elements for definite diagnosis	(1) Occult onset during puberty, more common in males (2) Localized muscular atrophy and weakness of the upper extremities,	(1) Atrophy or thinning of the middle and lower cervical spinal cord on either neutral or flexion MRI (2) LOA or the presence of a crescent-shaped high-intensity mass at the posterior	(1) Neurogenic lesions located in anterior horns and/or roots of the middle and lower cervical spinal cord (2) Normal or only mild abnormal conduction

	predominantly in the ulnar forearms and the intrinsic muscles of the hands unilaterally or mainly on one side (3) Absence of cranial nerve involvement and muscular atrophy in other parts of the body such as the lower limbs	epidural space on T2WI	velocity in peripheral nerves of the upper limbs
Other elements	(4) Cold paralysis and tremors in fingers when they are stretched (5) Active deep tendon reflex and/or positive pathological signs in anatomic parts of patients (6) Mild sensory deficits in the upper limbs in a small number of patients	(3) Anterior displacement and flattening of the lower cervical spinal cord and narrowing or absence of the anterior spinal space on neck flexion MRI (4) High-intensity signs located in the anterior horn areas on T2WI in parts of patients (5) Straight alignment or kyphosis of the cervical spine in X- rays in parts of patients	(3) Absence of obvious involvement of the cranial nerves and the thoracic, lumbar or sacral spinal cord
Definite HD	Meeting criteria 1,2,3	Meeting 1 or 2	Should meet 1,2 and 3
Probable HD	Meeting 2 and 3		Meeting 3

Clinical classification (40)

There is wide variability in the clinical manifestation and severity between HD patients. The crucial understanding of the severity of stage of HD patients influence the intervention options. Hence an attempt was tried to clinically classify and evaluate HD patients. Type I patients have atrophy of hand and forearm muscles unilaterally or with asymmetric involvement. They are further subdivided into stable or progression period subtype. Type II patients display atrophy of inner hand muscles and forearm in the upper limb (unilateral or asymmetric) as well as upper motor neuron signs (brisk knee reflex and positive Hoffmann signs). Type III represents atypical HD which includes proximal upper limb muscle involvement, symmetrical and bilateral muscle atrophy and sensory disturbances.

Table 2.3 - The Huashan clinical classification system for HD and the suggestions of treatment

Type	Clinical manifestations	Progression in the past 6 Months
I	Hand inner muscle and forearm muscle atrophy in unilateral upper limb or asymmetrical bilateral upper limbs	I a: stable period I b: progression period
II	Hand inner muscle and forearm muscle atrophy in unilateral upper limb or asymmetrical bilateral upper limbs with pyramidal tract injury	
III	Atypical HD, including upper limb proximal muscle atrophy, amyotrophy of symmetrical bilateral upper limbs, and sensory deficits with upper limbs	

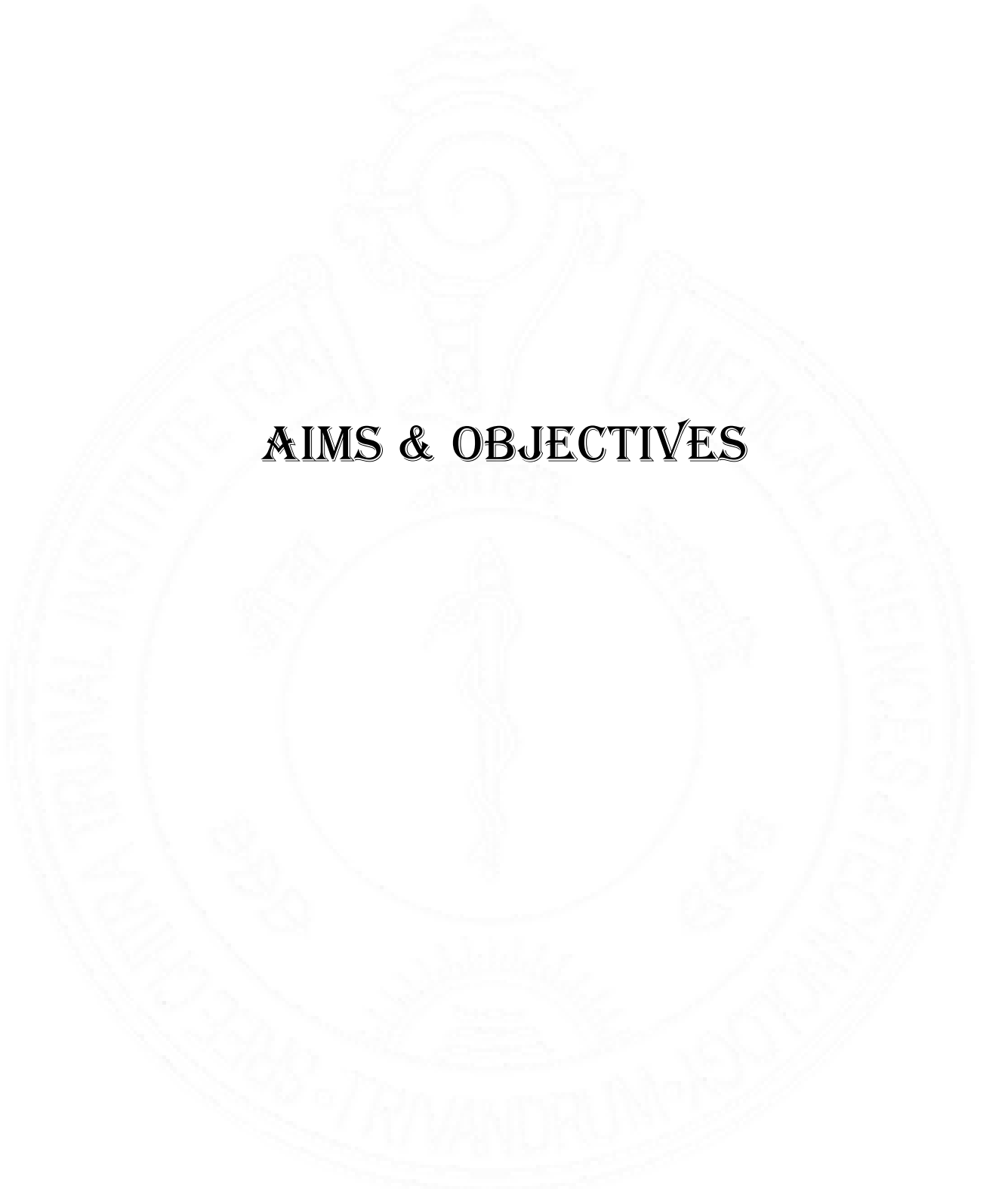
Treatment

The disease is self limiting after a short period of progression in most patients. Treatment is aimed at preventing the progression of disease before disability is established. No consensus is present regarding the management of HD. Application of hard cervical collar is the most commonly employed method and has been thought to prevent disease progression by restriction of neck movements (90). Tomkar et al showed that there was decrease in disease duration and improvement of weakness and cold paresis after applying cervical collar (90). Narayana et al also showed similar results (91). Early diagnosis is important and use of early clinical intervention might reduce the disability that develops in adolescent patients.

Surgical intervention is required when there is a rapid progression of severe disease, positive pyramidal signs, failure of conservative treatment and poor compliance to the neck collar (8). There are many anterior and posterior neck approaches described in various studies. The surgical approaches described in the literature include laminectomy, duraplasty, corpectomy, discectomy, decompression and spinal fusion (92,93,94,95). A meta-analysis on the impact of various surgical procedures in patients with HD described 10 neurosurgical procedures; the most commonly performed was anterior cervical discectomy and fusion (ACDF) followed by plating (96).

Prognosis

HD is a predominantly self-limiting disease with progression over 3–5 years and then plateaus. Cervical collar treatment improved 57.2% of patients (20). However, the patients who develop spasticity or other pyramidal signs, and those with a snake-eye appearance on MRI, tend to have poor outcome.



AIMS & OBJECTIVES

OBJECTIVES

- To assess the clinical characteristics of patients with Hirayama Disease.
- To evaluate the investigative parameters, radiological and electrophysiological, pertaining to the diagnosis of Hirayama disease.



METHODOLOGY

METHODOLOGY

Study Design:

The study was a descriptive observational single centre study by review of case records

Study setting

The study was conducted in Sree Chitra Tirunal Institute for Medical Sciences and Technology, Trivandrum

Study duration

The study was done during the time period of one year from January 2013 till July 2023

Study Participants

Inclusion criteria

All patients fulfilling the Huashan diagnostic criteria (Table 2.1) for Hirayama disease were included in the study. (4)

Exclusion criteria

1. Patients with alternate etiology for anterior horn cell disease such as amyotrophic lateral sclerosis or syringomyelia or alternate diagnosis such as motor neuropathies.
2. Radiological evidence of cervical spondylotic myelopathy
3. A detailed evaluation had not been performed to rule out alternate diagnosis

Sample size

All consecutive patients who fulfilled the criteria in the study period were included.

Ethical approval

The study commenced after the approval from the Institutional Ethics Committee of SCTIMST. Consent waiver was obtained. (SCT/IEC/2097/AUGUST/2023). Consent waiver was obtained as the study was retrospective in nature.

Data collection

Patient selection

The data was collected in a predesigned structured data collection proforma from the database maintained in our department. We screened the case records of patients using the diagnostic keywords of ‘Hirayama disease’, ‘focal anterior horn cell disease’, ‘monomelic amyotrophy’, ‘bimelic amyotrophy’ or ‘cervical flexion myelopathy’ registered or followed up in the Neurology out-patient department from January 2013 to July 2023. We identified 106 patients, out of which 35 patients were excluded as they did not conform to the inclusion criteria. The data collected included the demographic profile, historical details, detailed clinical examination and radiological findings. Historical details with respect to age of onset of illness, duration, course of progression, affected side, pattern of weakness and wasting, and cold paresis was noted. Clinical examination findings including laterality of involvement, pattern of wasting, tone and deep tendon reflexes, and tremors were recorded.

Electrophysiological evaluation

Detailed electrophysiological data was collected by reviewing the original reports. The details of motor conduction studies and F wave parameters were noted from median and ulnar nerves of both upper limbs and peroneal and tibial nerves of the lower limbs for all patients. Additional radial nerve and proximal upper limb motor studies were noted where available. Compound muscle action potential (CMAP) values from abductor pollicis brevis (APB) and abductor digiti minimi (ADM) were used to ulnar-median CMAP ratio for the affected limbs. Sensory conduction studies from median, ulnar, sural and superficial peroneal nerves were noted.

Electromyography performed as a part of the evaluation was recorded with regard to the myotome involvement, denervation and reinnervation patterns. The pattern of distal and proximal involvement was specifically analysed.

Radiological evaluation

Details of dynamic MRI (neutral, flexion and extension) imaging studies with/without contrast was recorded. Recording pertaining to cervical cord changes during neck flexion compared to neutral MRI was done.

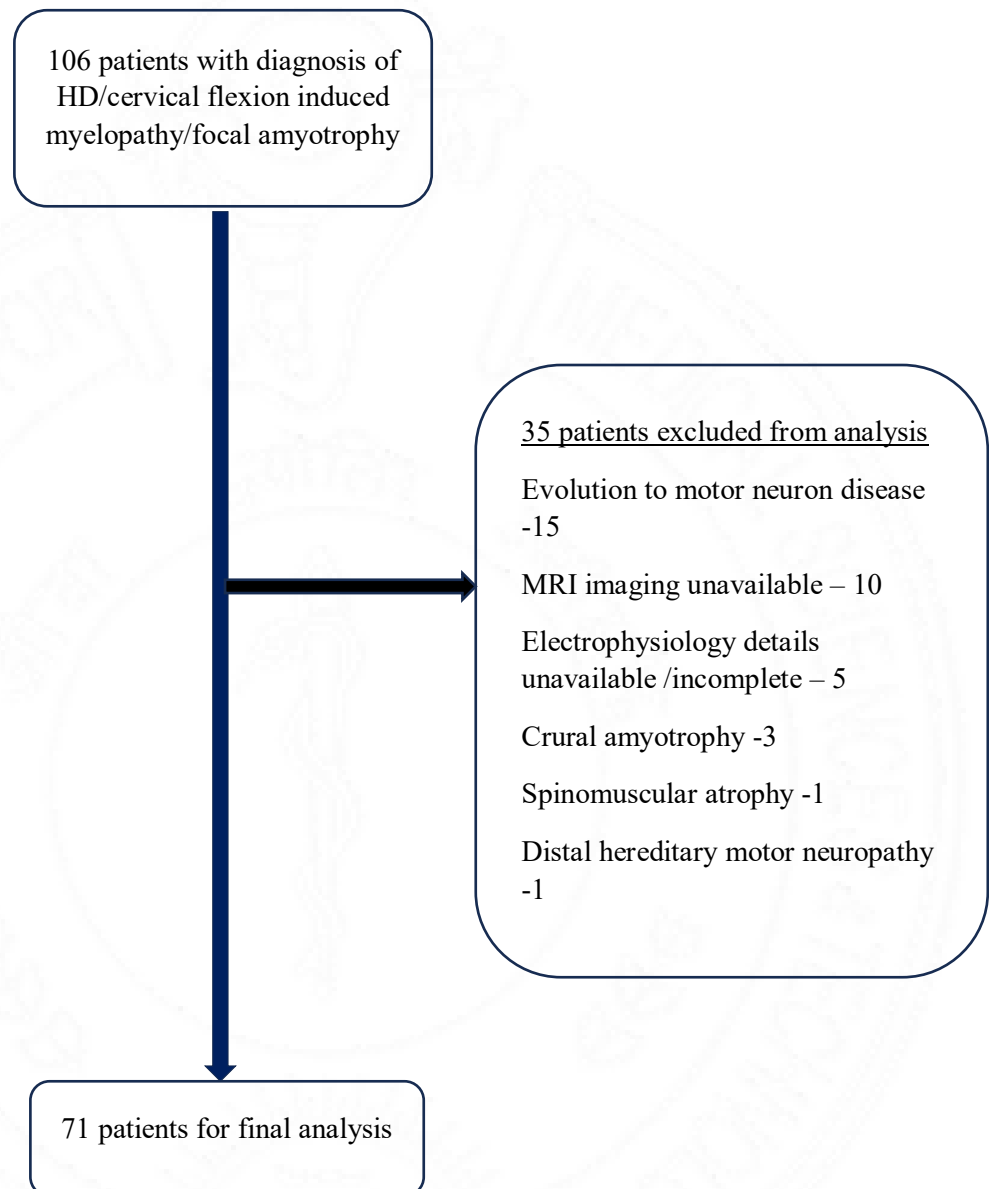
Statistical analysis

For statistical analysis, we used proportion as a descriptive statistic for categorical and ordinal variables, median and interquartile range for ordinal and continuous variables, and mean (SD) for continuous variables. Categorical variables were analyzed using the Chi-square test. Analyses was performed using statistical software IBM SPSS Version 22.

RESULTS

RESULTS

Figure 5.1 - Trial profile of the study



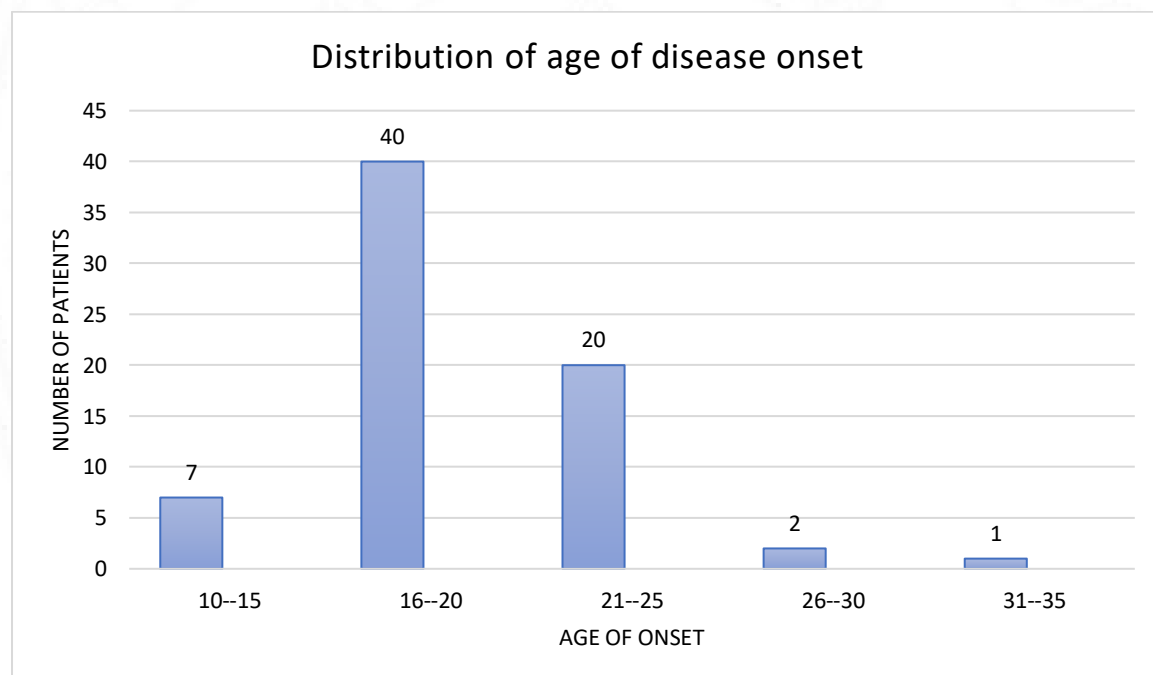
We identified and reviewed 106 case records of patients with diagnosis of focal anterior horn cell disease or HD. Among them, 35 patients who had incomplete diagnostic details or with alternate diagnosis during the last recorded follow up were excluded. The final analysis included 71 patients.

Clinical characteristics

All but one of the 71 patients were males (n=70, 98.5%). The mean age of patients was 19.1 ($\pm$ 3.86) years. 28 (39.4%) patients were below 18 years of age.

The median duration of illness at diagnosis was 2 (0.3 -14) years. Clinical characteristics have been summarised in Table 5.4.

Figure 5.2 - Bar chart showing the age distribution in the study cohort

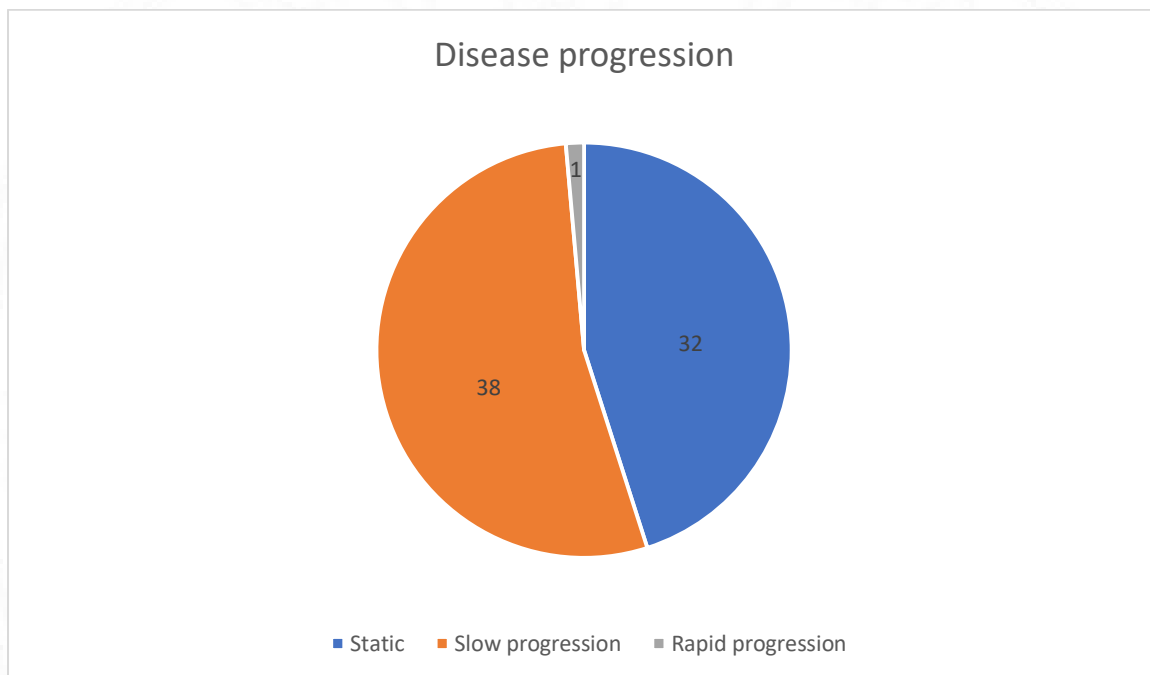


Disease course

Table 5.1 – Descriptive analysis of the disease progression

Disease course	Number(n)	Percentage (%)
Static	32	45.1
Slowly progressive	38	53.5
Rapidly progressive	1	1.4

Figure 5.3 - Pie chart showing the disease progression



48(67.6%) patients had unilateral symptoms at onset. Most of patients presented with left upper limb symptoms.

Figure 5.4 – Pie chart showing the laterality of involvement at presentation

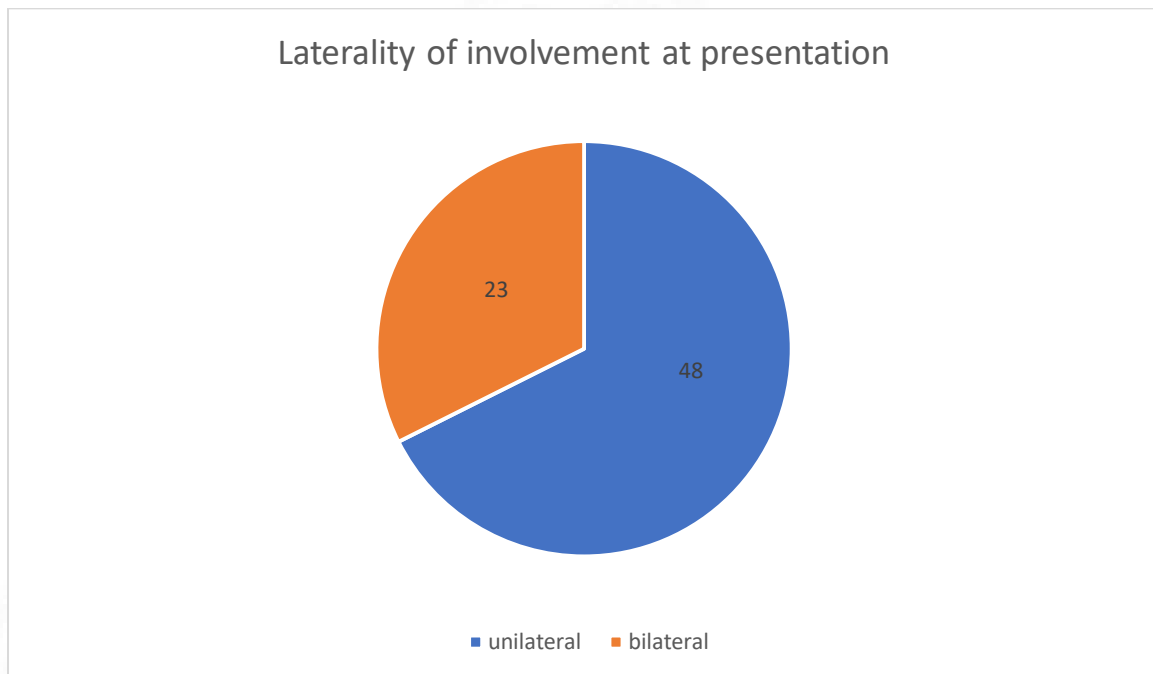
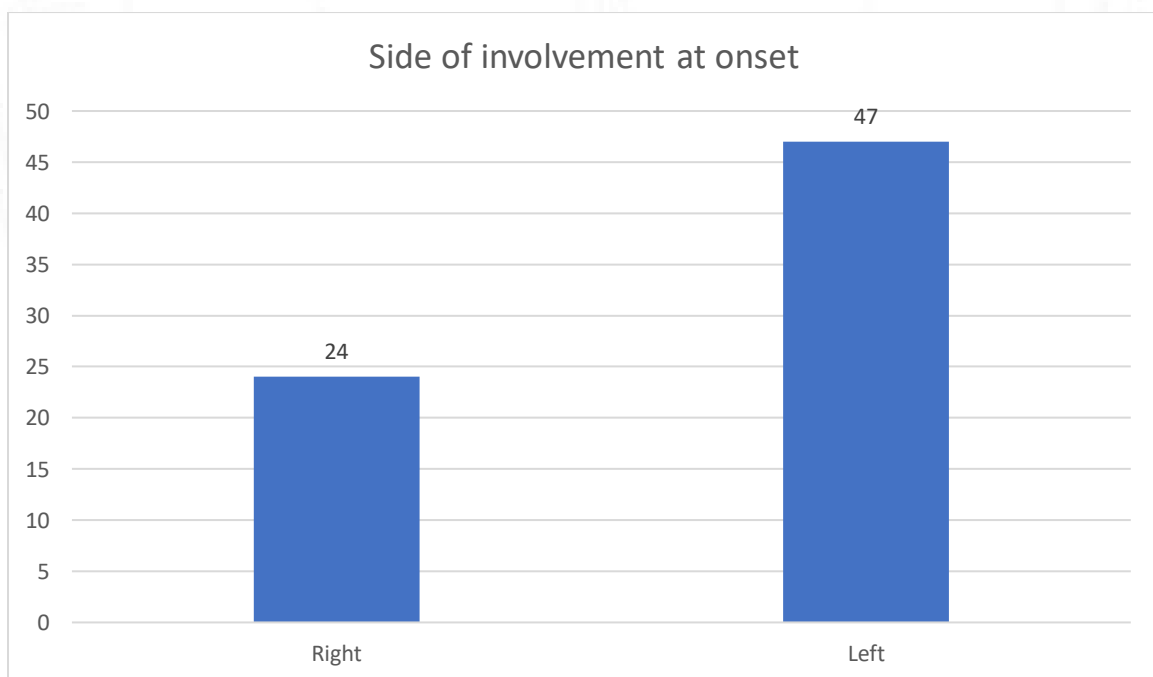


Figure 5.5 – Bar chart showing the side of involvement



A. Clinical Symptoms

All patients had upper limb symptoms at onset. In our patients, the first reported symptom was weakness in 53 (74.6%) patients, wasting in 7 (9.8%) patients and tremors in 11(15%) patients.

Figure 5.6 – Bar chart showing the initial symptom at onset

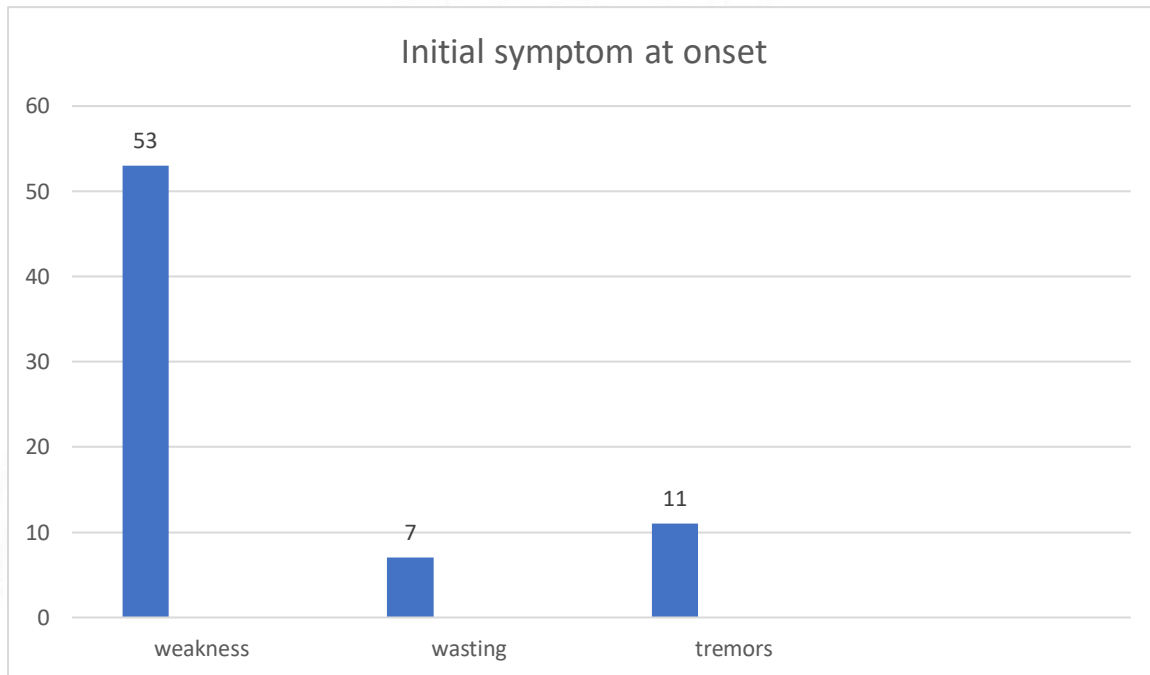


Table 5.2 – Descriptive analysis of clinical symptoms

Parameter	Frequency(n)	Percentages(%)
Fasciculations	24	33.8
Cold paresis	14	19.7
Tremors	49	69
Neck pain	10	14
Cramps	4	5.6

The most frequent symptom apart from weakness and wasting was tremors involving upper limbs. Family history of similar illness among family members was reported by 2(3%) patients. Son mother duo had presented with similar unilateral weakness and wasting in the upper limb. Mother had undergone cervical laminectomy for her complaints in the remote past. Both had no progression of symptoms. The second familial trait was observed in father and son who had unilateral weakness and wasting of upper limb with a static course.

B. Clinical examination findings

In our study cohort, we observed that 26 (37%) patients had unilateral weakness on examination. Bilateral involvement was detected in 45 (63.3%) patients among whom 38(84%) patients exhibited asymmetry of symptoms. It was interesting to note that though 48(67.6%) patients had presented with unilateral symptoms, on examination 22 (46%) of them had mild weakness on the contralateral side as well.

Figure 5.7 – Bar chart showing pattern of weakness

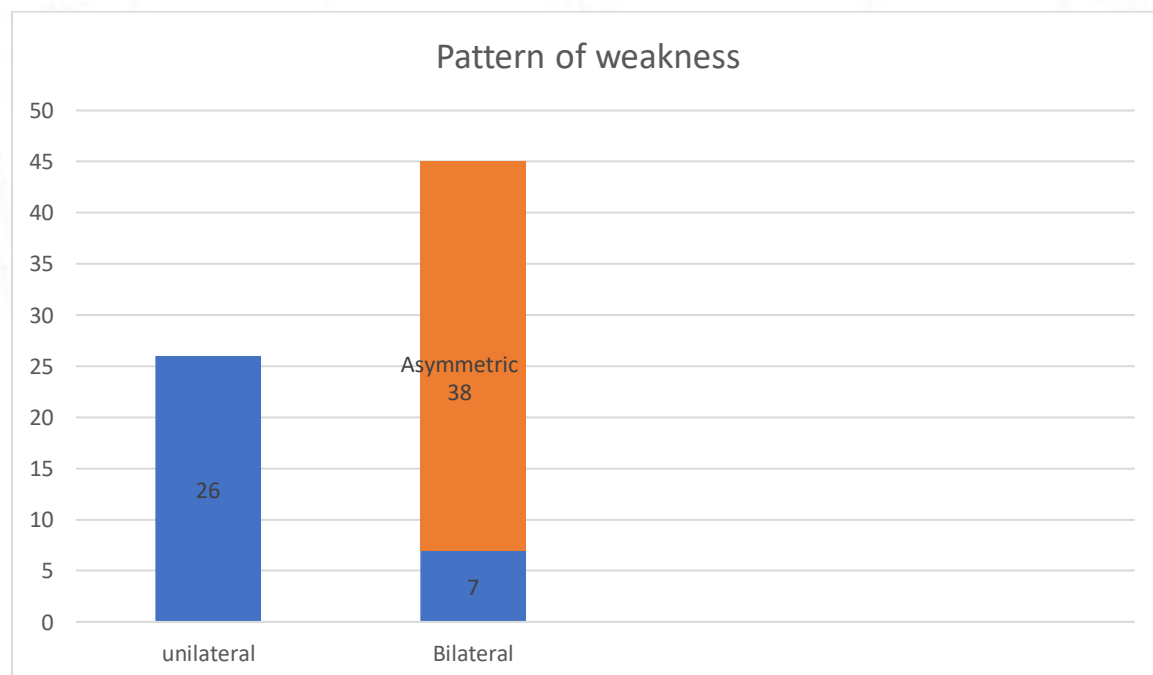
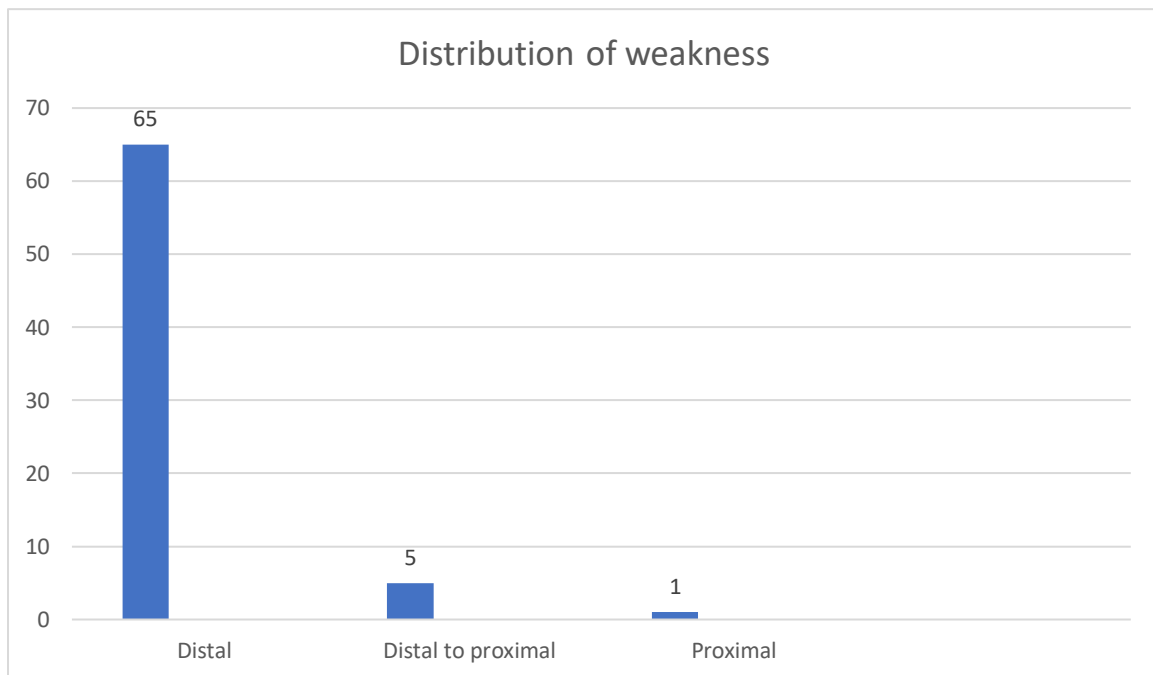


Figure 5.8 -Bar chart showing distribution of weakness



Distal upper limb weakness was the most frequently detected pattern. In addition, proximal involvement was noted in 6(8.4%) patients with 5(84%) patients having distal to proximal progression (Fig -5.8). The mean MRC (modified) sum score was 75.3 ± 3.11 .

Figure 5.9 – Distribution of MRC (modified) sum score

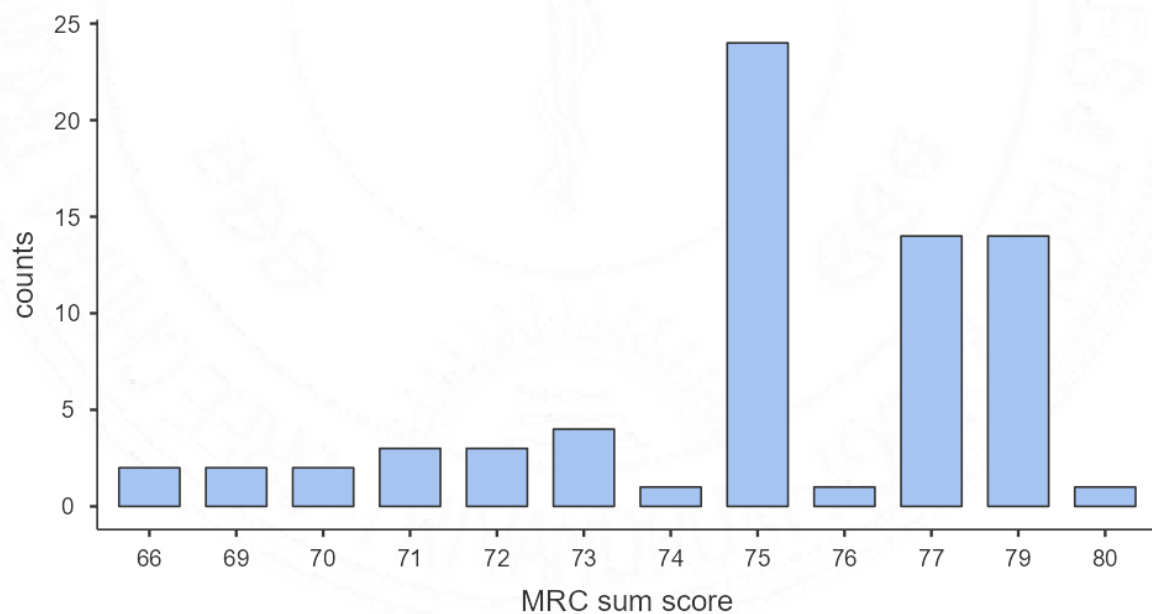
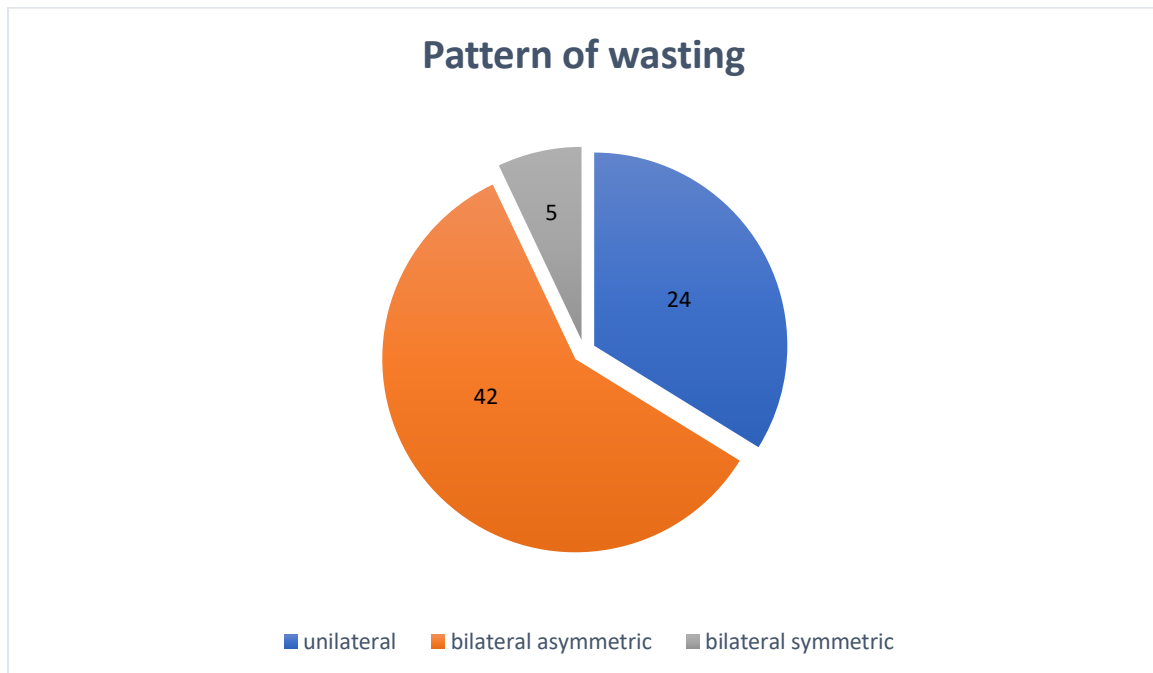


Figure 5.10 – Pie chart showing pattern of wasting



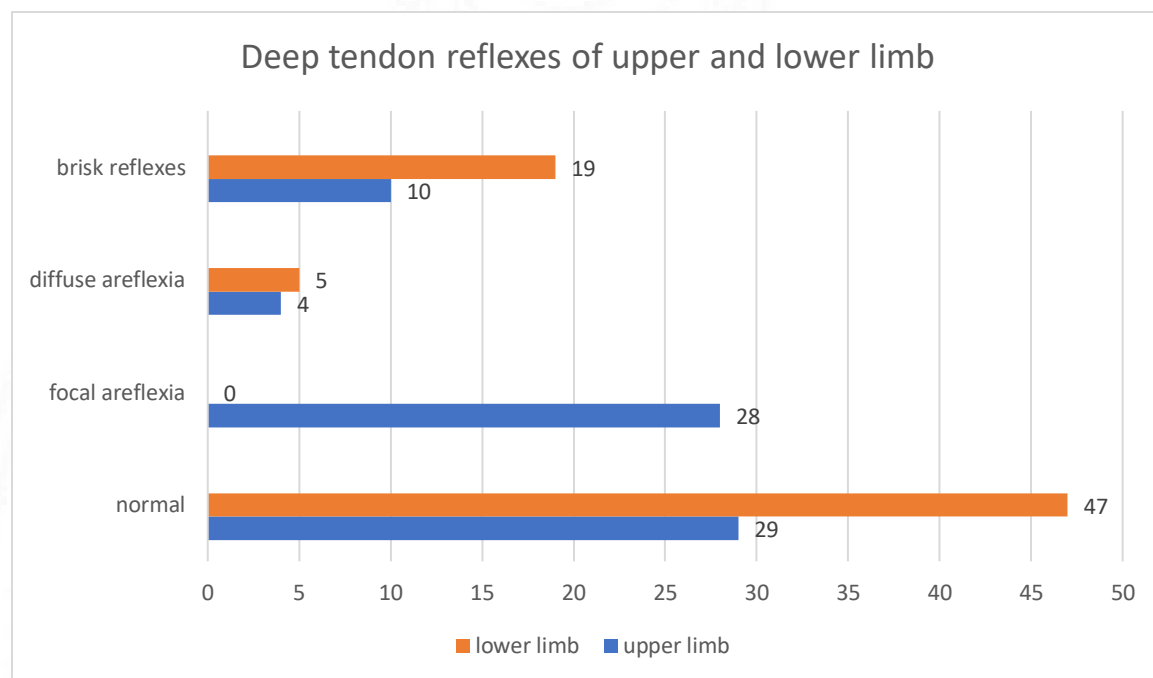
Unilateral wasting of upper limbs was seen in 24 (34%) patients while 47(66%) patients had bilateral wasting with asymmetric pattern observed in 42(89.3%) patients. Lower limb wasting was observed in one patient.

Table 5.3 – Descriptive analysis of pattern of wasting

Muscles involved	Number	Percentage(%)
Intrinsic hand muscles	16	22.5
Intrinsic + forearm	34	47.9
Intrinsic + forearm + arm	8	11.3
Intrinsic + forearm + arm + shoulder	11	15.5
Shoulder	1	1.4
Intrinsic + shoulder	1	1.4

Distal wasting was observed in 50 (70%) patients. Atypical finding of proximal involvement was seen in 21(30%) patients. It was interesting to note that while proximal weakness was present in only 6 (8.4%) patients, proximal wasting was detected in 21(29%) patients. Other findings including hypotonia was observed in 31(44%) patients.

Figure 5.11 – Bar chart showing deep tendon reflexes of upper and lower limb



Deep tendon reflexes of upper limb showed areflexia (n-32, 45%) as the most common abnormality followed by normal and brisk reflexes in 29 (41%) and 10 (14%) patients respectively. Lower limb reflexes were exaggerated in 19 (27%) patients. Hand tremors was the most frequent observed clinical finding. (n-48, 67.6%)

Figure 5.12 – Pie chart showing hand tremors



Table 5.4 – Summary of clinical characteristics

Mean age at onset (years)	19.1 ($\pm$ 3.86)
Male: Female	70:1
Median duration of illness at diagnosis (years)	2 (0.3 -14)
Clinical parameters	Number (%)
Disease course	
Static	32(45)
Slowly progressing	38(54)
Rapid progression	1(1.4)
Laterality of symptom onset	
Unilateral	48(67.6)
Bilateral	23(32)
Side of involvement	
Right	24(34)
Left	47(66)
Initial symptom	
Weakness	53(75)
Wasting	7(9.8)
Tremors	11(15.4)
Cramps	4(5.6)
Cold paresis	14(20)
Fasciculations	24(34)
Tremors	49(69)
Neck pain	10(14)
Family history	2(2.8)
Weakness on examination	
Unilateral	26(37)
Bilateral	7(9.8)

Asymmetric	38(53.5)
Pattern of weakness	
Distal	65(91.5)
Distal to proximal	5(7)
Proximal	1(1.4)
Mean MRC sum score	75.3 ± 3.11
Wasting	
Unilateral	24(34)
Bilateral	5(7)
Asymmetric	42(59)
Proximal wasting	
Yes	21(30)
No	50(70)
Pattern of wasting	
Intrinsic	16(23)
Intrinsic + forearm	34(48)
Intrinsic + forearm + arm	8(11)
Intrinsic + forearm + arm+ shoulder	11(15)
Shoulder	1(1.4)
Intrinsic + shoulder	1(1.4)
Tone	
Normal	40(56.3)
Decreased	31(43.7)
Deep tendon reflexes - Upper limb	
Normal	29(41)
Focal areflexia	28(39)
Diffuse areflexia	4(5.6)
Exaggerated	10(14)
Deep tendon reflex - Lower limb	
Normal	47(66)
Sluggish	5(7)
Exaggerated	19(27)
Hand tremors	48(67)

Electrophysiology

Nerve conduction study (NCS) was found to be abnormal in 37 (51.3%) patients. Ulnar nerve CMAP reduction was the most frequent abnormality (n = 30, 42.2%).

Figure 5.13 – Pie chart showing reduced CMAP in nerves of upper limb

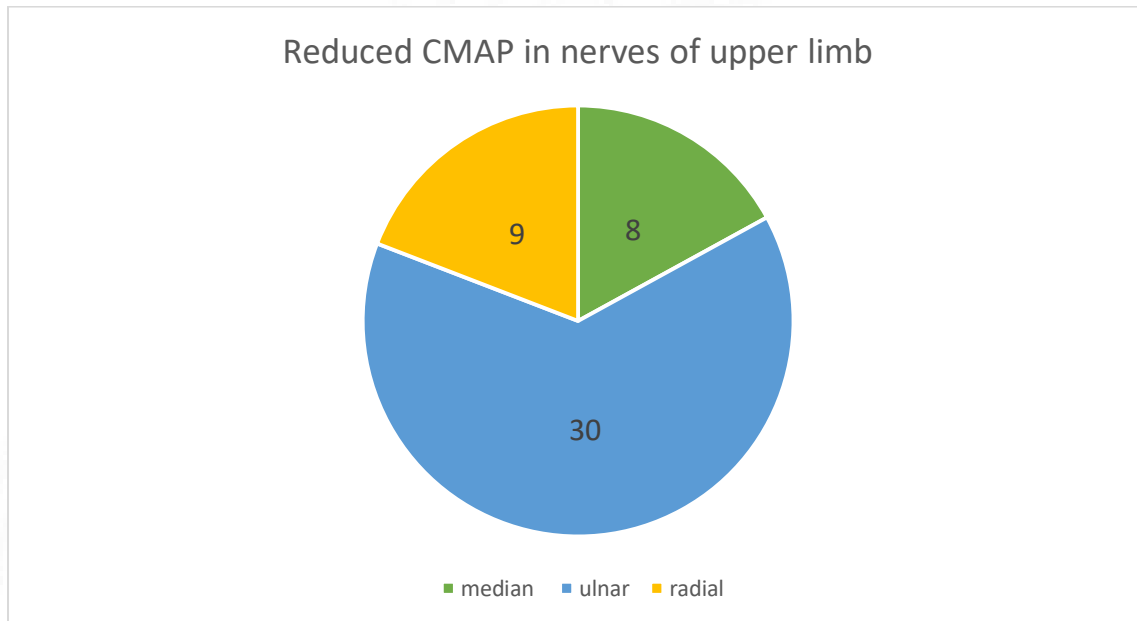


Figure 5.14 – Bar chart showing F wave abnormalities in median nerves

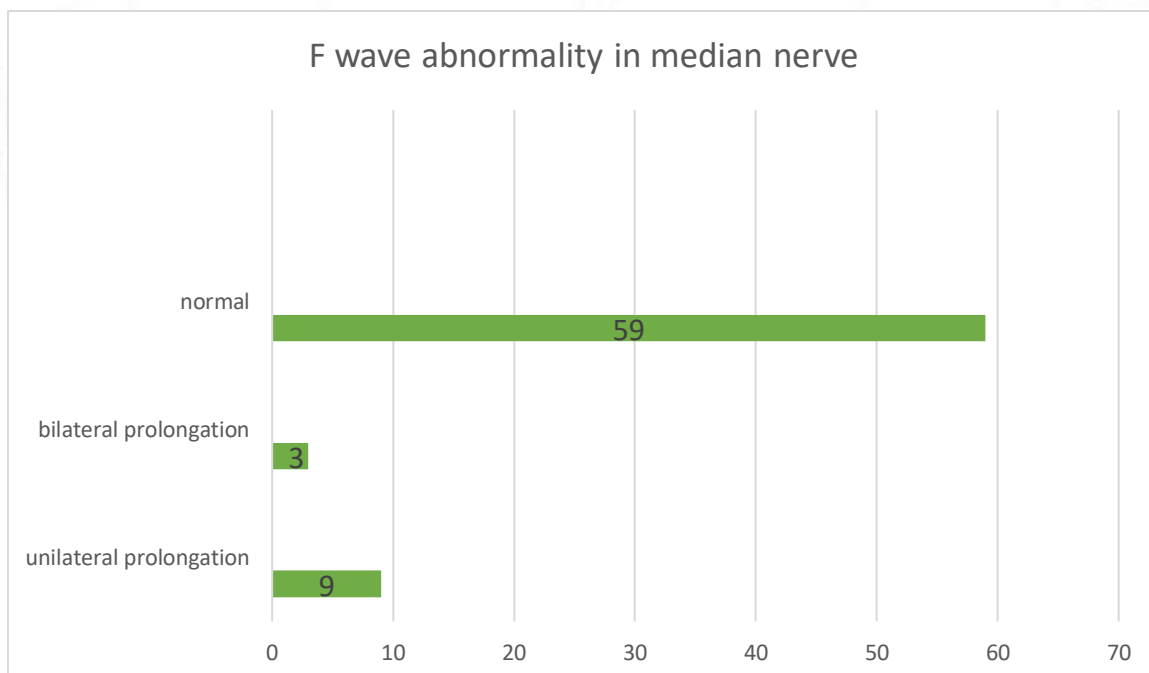
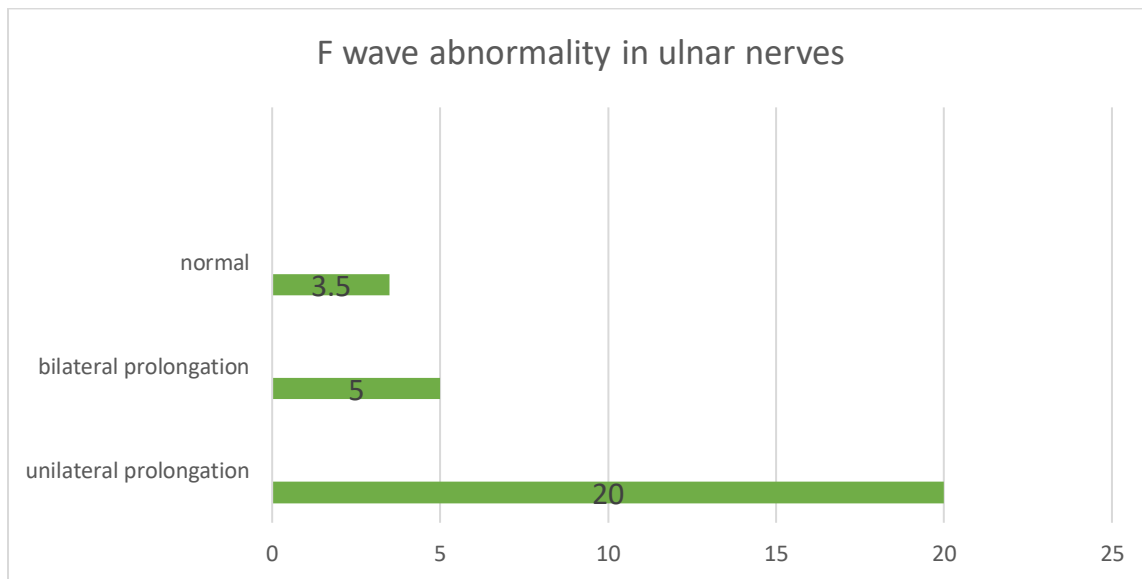
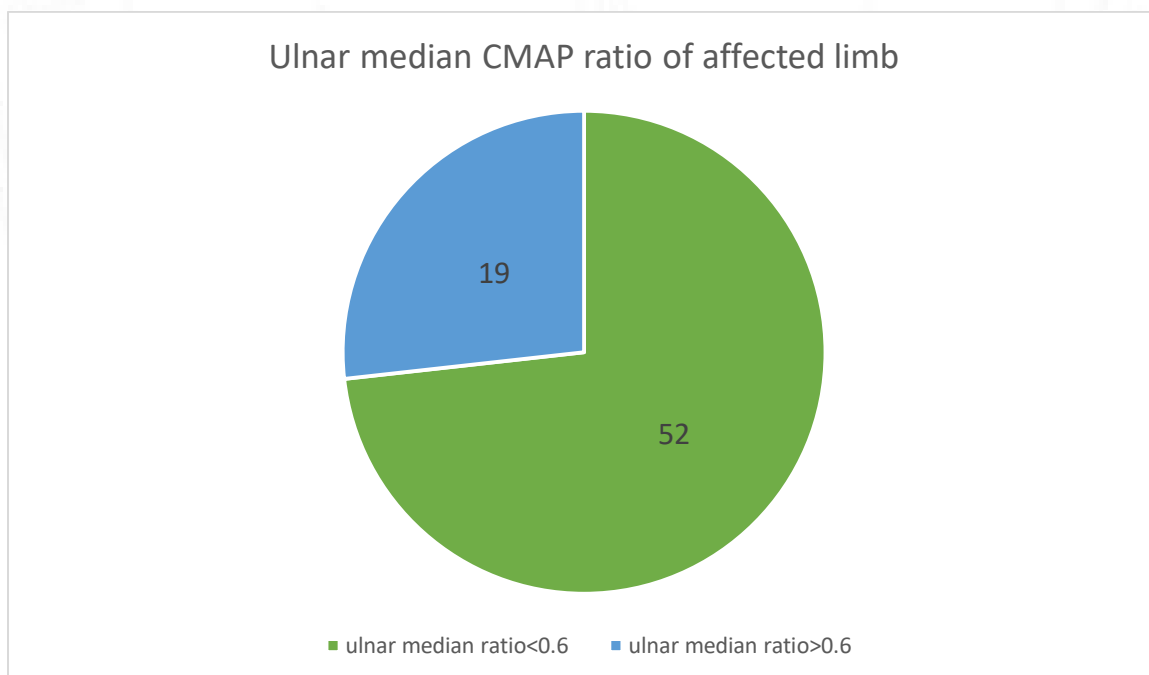


Figure 5.15 – Bar chart showing F wave abnormalities in ulnar nerves



F wave abnormality was most commonly noted in ulnar nerves (n-25, 35.2%) followed by median nerves (n-12,16.9%). The mean ulnar median CMAP ratio on the affected side was 0.49 ± 0.37 which conformed to the reverse split hand equivalent. On the unaffected limb was 1.26 ± 0.49 . 52 (73.2%) patients had ulnar median CMAP ratio < 0.6 .

Figure 5.16 – Pie chart showing ulnar median CMAP ratio < 0.6



Electromyography abnormalities were noted in all patients. Abnormalities were more frequently appreciated in both limbs (n-63, 88.7%), the common observation being asymmetric involvement (n-45, 63.3%). In the distal cervical segments (C7-T1), denervation potentials which included fibrillations, positive sharp waves, fasciculations were observed in 66 (92.9%) patients and reinnervation potentials in 61(85.9%) patients.

Figure 5.17– Pie chart showing pattern of EMG changes in the upper limb

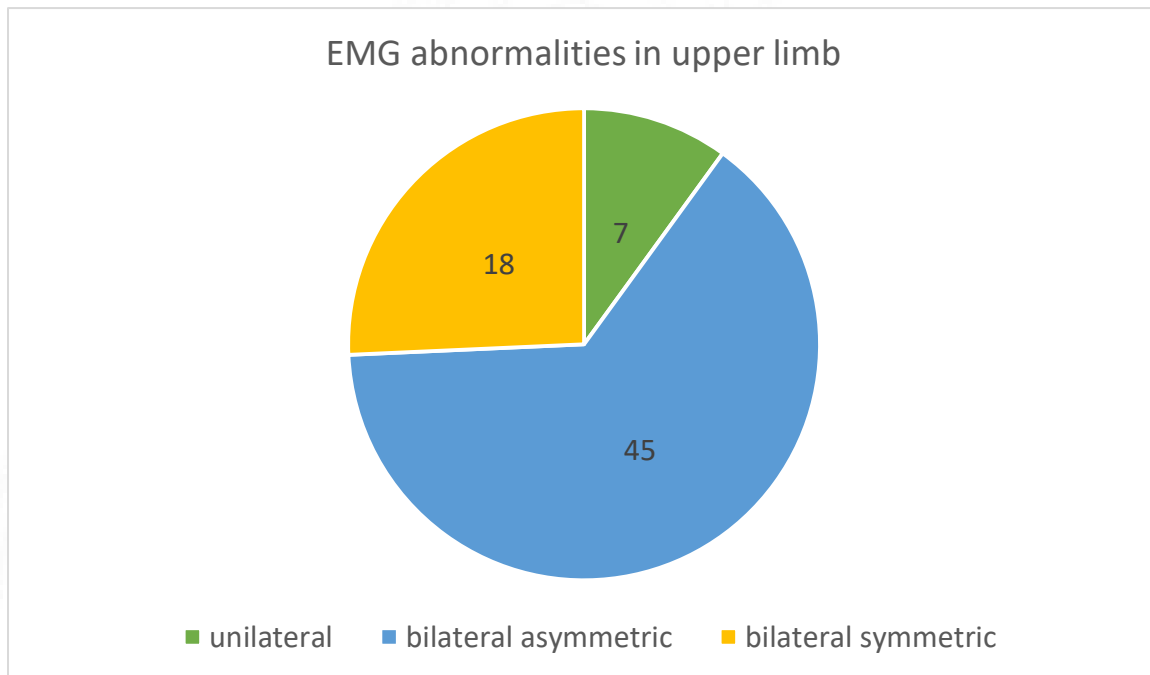


Figure 5.18 – Bar chart showing distribution of EMG changes in upper limb

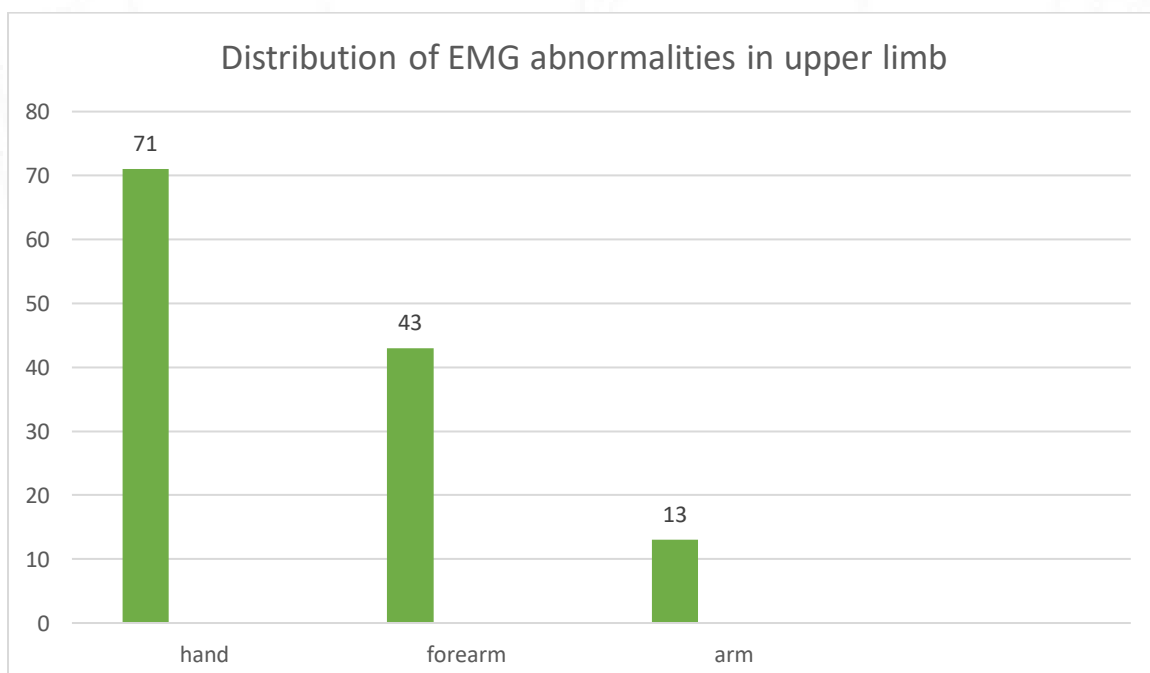


Figure 5.19 – Bar chart showing denervation and reinnervation potentials across the cervical segments

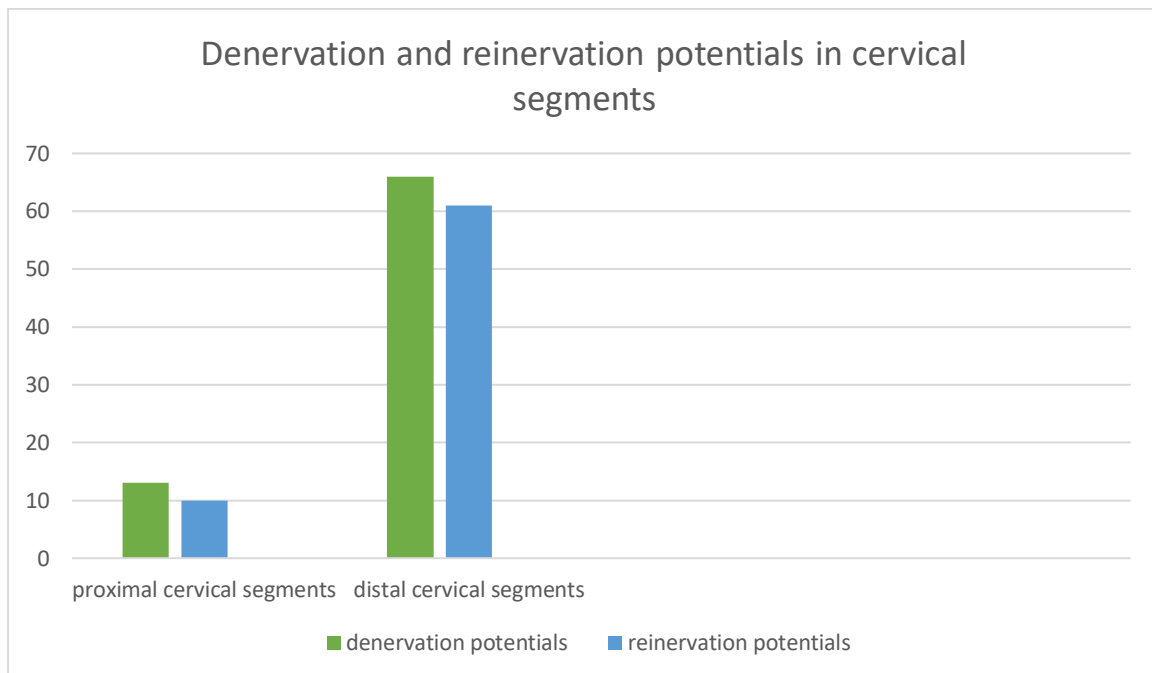
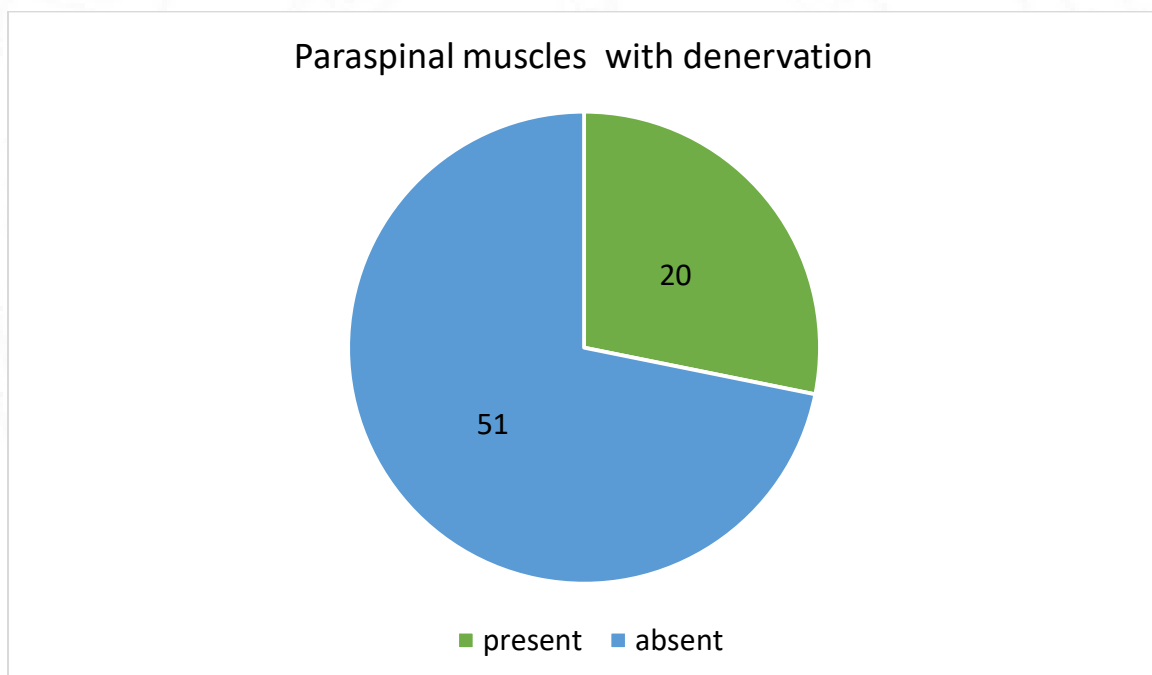


Figure 5.20 – Pie chart showing denervation potentials in paraspinal muscles



EMG changes in proximal cervical segments were noted in 23 (32.3%) patients. Among them, denervation potentials were recorded in 13 (18.3%) patients and reinnervation in 10 (14%) patients. The median number of paraspinal muscles sampled was 2 (range 1-8). Paraspinal

denervation potentials were present in 20 (28.2%) patients. Electrophysiologic abnormalities have been summarised in table 5.5.

Table 5.5 – Summary of electrophysiology characteristics

Electrophysiology parameters	Number (Percentage)
Motor CMAP	
Reduced median CMAP	8(11.2)
Reduced ulnar CMAP	30(42.2)
Reduced radial CMAP	9(12.6)
Median reverse split hand ratio of the affected limb	0.49 ± 0.37
F wave abnormalities of median nerve	
Unilateral prolongation	9(12.6)
Bilateral prolongation	3(4.2)
Normal	59(83)
F wave abnormalities of ulnar nerve	
Unilateral prolongation	20(28)
Bilateral prolongation	5(7)
Normal	46(65)
Pattern of EMG abnormalities	
Unilateral	7(9.8)
Bilateral	
Asymmetric	45(63.3)
Symmetric	18(25.3)
Lower cervical segments - C7 -T1 segments	
Denervation pattern	66(93)
Reinnervation pattern	61(86)
Proximal cervical segments	
Denervation pattern	13(18)
Reinnervation pattern	10(14)
Paraspinal muscle EMG	
Denervation pattern	20(28)

Radiological characteristics

MRI cervical spine with dynamic studies were performed in all patients, out of which contrast studies were done in only 34 (47.8%) out of 71 patients. In them, the most commonly recurring abnormality was thinning of cervical cord (n – 46, 64.7%) followed by loss of cervical lordosis (n – 41, 57.7%). Thinning of cord varied from C2 -T1 segments, most common site of involvement being upper cervical cord. (n-15, 32.6%) Other striking abnormalities included hyperintensity in anterior horn cells, enhanced epidural crescent in flexion, anterior displacement of dura in flexion was noted in 29 (40.8%) patients each. Hyperintensities in anterior horn cells were maximally appreciated in the C4 – C7 segments in 16 (55.1%) patients. Cervical disc disease was present in 19 (26.7%) patients. Disc disease was not severe enough to produce the clinical symptoms.

Radiological abnormalities observed in our cohort has been summarised in table 5.6

Figure 5.21 – MRI abnormalities on neutral position

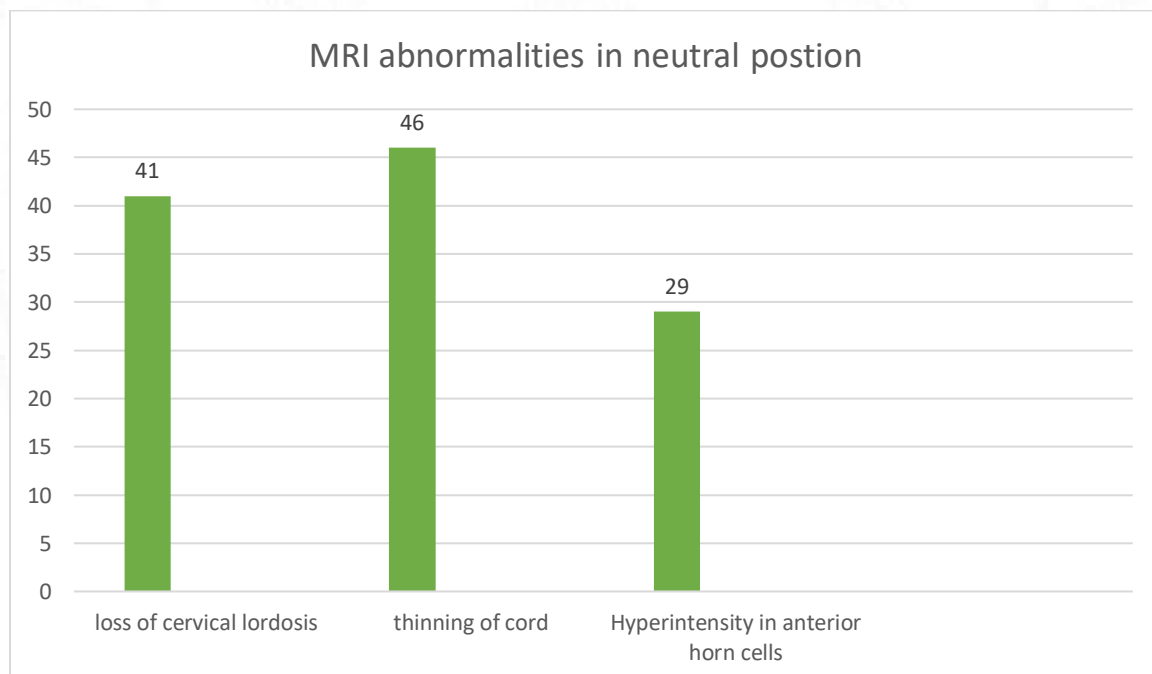


Figure 5.22 – MRI abnormalities on neck flexion

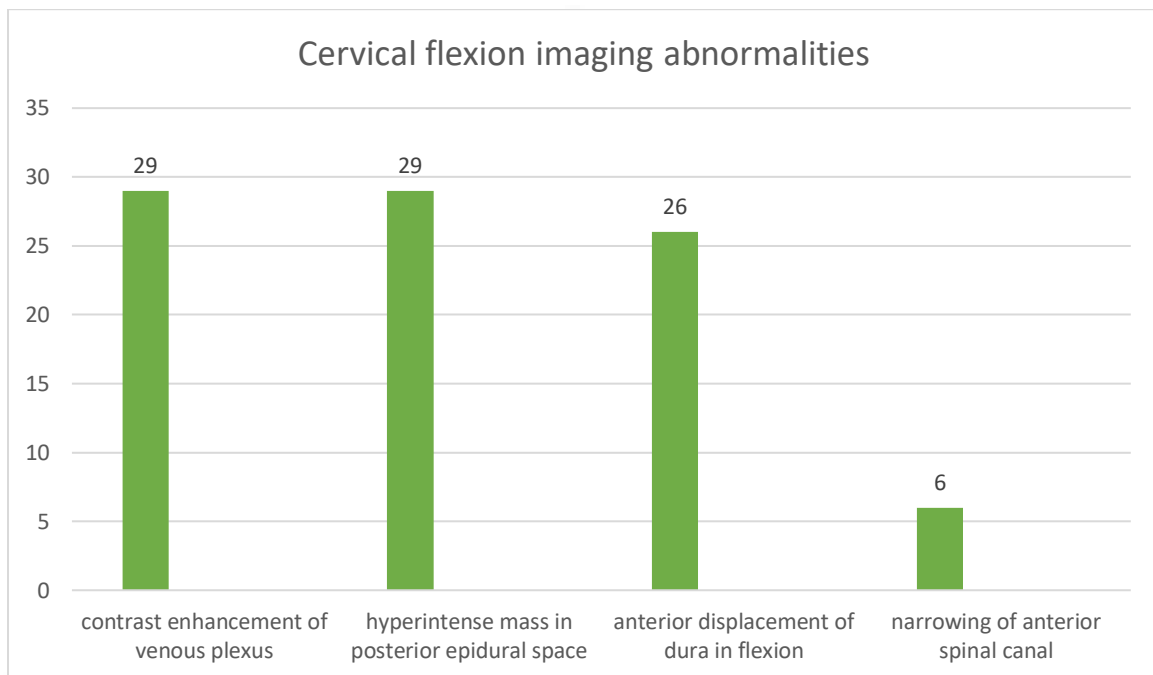


Figure 5.23 – Distribution of MRI hyperintensity in anterior horn cells

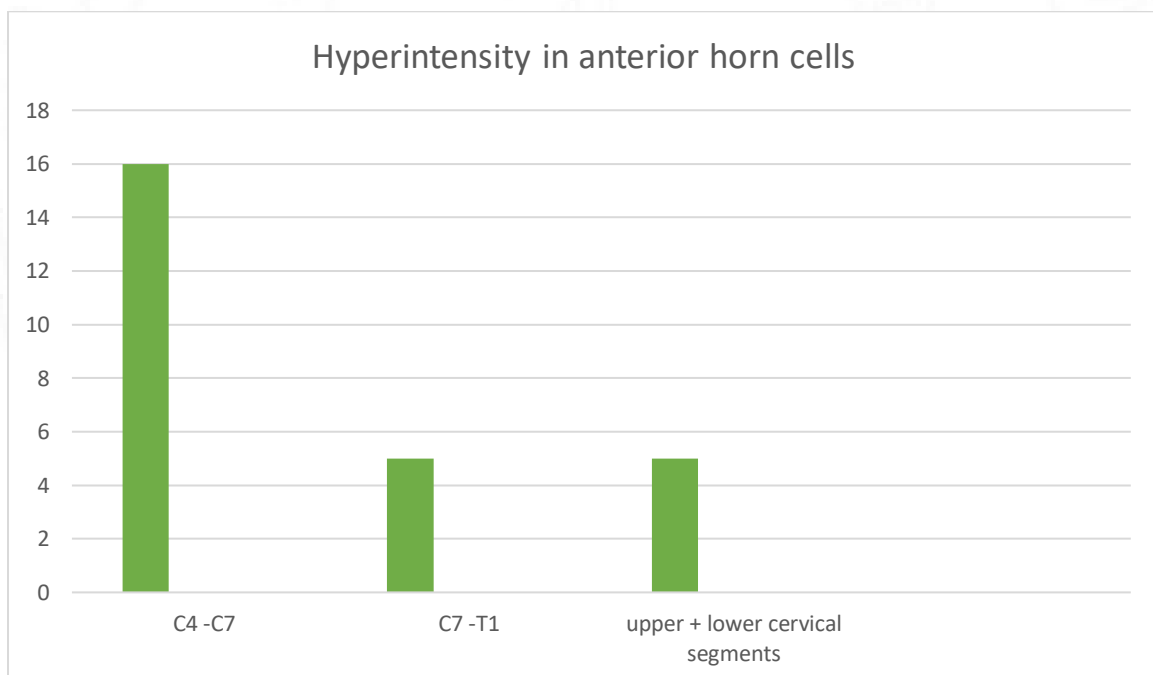


Table 5.6 – Summary of radiological findings

Imaging findings	Number(Percentage)
MRI cervical spine with contrast – dynamic studies	
Yes	34(47.8)
No	37(52.1)
Loss of cervical lordosis	41(58)
Thinning of cord	46(65)
Hyperintensity in anterior horn cells	29(41)
Contrast enhancement (venous plexus)	29(41)
Hyperintense mass in posterior epidural space	29(41)
Anterior displacement of dura in flexion	26(37)
Narrowing of anterior spinal canal in flexion	6(8.4)
Cervical disc disease	19(27)

Table 5.7 – Comparison of static versus slow progressor

		Static	Slow progressors	P value
Proximal weakness	Y	3	3	0.800
	N	29	36	
Proximal wasting	Y	10	11	0.78
	N	22	28	
Tremors	Y	24	25	0.323
	N	8	14	
Cold paresis	Y	6	8	0.853
	N	26	31	
Fasciculations	Y	11	13	0.926
	N	21	26	
Neck pain	Y	4	6	0.728
	N	28	33	
Polyminimyoclonus	Y	24	24	0.228
	N	8	15	
Ulnar/median CMAP ratio of affected limb (<0.6)	Y	21	31	0.189
	N	11	8	

Ulnar/median CMAP ratio of unaffected limb(<0.6)	Y N	14 18	18 21	0.839
EMG – forearm muscles	Y N	22 10	21 18	0.201
EMG – arm muscles	Y N	4 28	3 39	0.499
Loss of cervical lordosis	Y N	22 10	19 20	0.08
Hyperintensity in anterior horn cells	Y N	12 20	17 22	0.603
Contrast enhancement (venous plexus)	Y N	17 15	12 27	0.050
Anterior displacement of dura in flexion	Y N	15 17	11 28	0.104
Narrowing of anterior spinal canal in flexion	Y N	3 29	3 36	0.800
Cervical disc disease	Y N	6 26	13 26	0.167

We observed a statistically significant association between disease course and contrast enhancement of venous plexus. (p-0.05)



DISCUSSION

DISCUSSION

Our study highlights the varied clinical, electrophysiological and radiological characteristics from south Indian population.

Demographic characteristics

Like in other studies, males assumed the majority in our cohort with the exception of one. We had a higher ratio of males in comparison to 9:1 reported in another Indian study (66). Tashiro et al reported 10.8% females in his survey (20). The lower female preponderance was hypothesised due to the lower rates of annual body height growth and the slope of the growth velocity curve. Our hospital is a tertiary care referral centre, and the lower proportion of female patients in our sample may be explained by the peripheral hospitals' low index of clinical suspicion and the generally steady progression of the illness course.

28 (39.4%) patients had an adolescent onset of symptoms in our group. This finding was in tune with previous studies. The mean duration of illness at diagnosis was 2.49 ± 2.51 years which was nearly the same as in other Indian studies (66). The study conducted in China had a mean time to diagnose of 56.89 ± 52.4 months which was a little higher compared to our cohort (23).

Clinical characteristics

Bilateral asymmetric ($n = 42$, 59.1%) involvement of upper limbs appeared to be the core features in our cohort. The earliest reports on this rare disease had shown unilateral distal wasting and weakness (1,3,66). Though the patient only has unilateral presentation, but the finding of bilateral asymmetric involvement becomes an important finding that the clinician has to investigate. Tashiro et al observed that though 72% of his patients presented with unilateral symptoms bilateral involvement on examination was observed in 29 % of patients (20). Other Indian studies including large cohort of Nalini et al and smaller case series from India had shown bilateral involvement of 30 – 55% (66,70). This finding remains crucial to search for bilaterality despite the unilateral onset. Our study revealed that the initial symptom presentation may not always be weakness or wasting as tremors ($n=11$, 15.4%) of the upper

limbs emerged as yet another initial symptom. In most of the other studies importance was not attached to initial symptoms other than the classically described symptoms.

Though HD had been labelled as a self limiting disease in accordance to the results from Gourie-Devi et al, there are case series wherein around 7.5 % have reported progression beyond 5 or even 10 years. (26,24,49,55). 38 (53.5%) patients were slow progressors in our study and one had a rapid progression over initial 2 years. Study done from China had shown all patients to be slow progressors (23). The classical self-limited nature of the illness is questioned by the group of atypical HD whose progression can be halted with interventions. (8). Hence it becomes prudent to identify the HD patients who are likely to progress by a close clinical follow up.

Two cases with familial preponderance have been described in our study. Lyu F et al in the modified 3 round Delphi survey which culminated in the clinician led guideline for clinical practice in HD concluded that familial forms of HD are very rare and requires further evaluation (8). Nevertheless there have been some rare familial reports from India, China and Japan (6,7,20,23).

Tremors was the most frequent symptom, apart from the classical symptoms of weakness and wasting, in our study constituting 69% while cold paresis and fasciculations were the more common striking symptoms in other studies. The other salient symptoms which included cold paresis and fasciculations were less frequently reported in our study cohort. Cold paresis was a striking abnormality which was reported in the other Indian studies (16,26,66). The plausible explanation maybe that the patients in our part of the country are not exposed to the cold climate as in the geographical locations of the other studies. Fasciculations reported from other studies have been varying. Cramps have been more frequently reported from Indian studies but was comparatively less reported from our group (16).

Sensory symptoms which were present in our study included neck pain reported in 10 (14%) patients. Similar non-specific sensory abnormalities including pain in the limb, hyperhidrosis and hyperalgesia has been reported in as high as 23 % patients (16,23,66). However no objective findings on sensory examination has been the consistent norm in all the patients.

Distal muscle weakness of upper limbs was observed in 65(91.5%) which was congruent to the study by Nalini et al who had 204(91.1%) patients with distal weakness (66). However, we found proximal muscle wasting in 29% patients which is higher compared to the figures reported by Peiris et al and Hirayama et al (22,73). However, Nalini et al had 40% asymptomatic / symptomatic proximal wasting (66). Thus, our study highlights the prominent proximal affliction in the form of wasting that remains underappreciated by the patients. The pattern of wasting in our study has been strikingly asymmetric present in 42 (59.1%) patients. Asymmetry in weakness and wasting emerged as a distinguishing point from our study.

Polyminimyoelonus (67%) emerged as the most consistent clinical sign universally reported in almost all the studies and our study was no exception to that rule. Hypotonia was a less commonly observed finding in our group (43.6%) in contrast to study by Preetish et al wherein all patients had hypotonia (16). Though the classical findings of focal areflexia in the upper limb was elicited in 28 (39.4%) patients, atypical features of brisk reflexes in upper and lower limb were observed in 10(14%) and 19(26.7%) patients respectively. Similar findings have been observed by Nalini et al but Preetish et al recorded these atypical findings to the tune of 42- 52 % (16, 66). The variation maybe due to the variation in patient selection as Preetish et al's cohort comprised patients with distal bimelic amyotrophy phenotype (16). The phenotype of HD varies as has been observed from our cohort comprising distal monomelic amyotrophy, proximodistal amyotrophy, proximal bimelic amyotrophy, asymmetric segmental spinal muscular atrophy has a very wide spectrum. These varied phenotypes fall under the umbrella term of HD. The atypical findings of bilateral, proximal involvement, rapid progression (observed in one patient), positive family history stands distinct from the other studies.

Electrophysiological characteristics

Electrophysiology is an integral component which aids in ascertaining the diagnosis of HD. In our study, nerve conduction studies (NCS) were abnormal in 37 (52.1%) patients with the ulnar CMAP being the most commonly affected nerve. This is congruent to the previously published studies. (24, 82) The characteristic electroclinical correlate of reverse split hand index (ulnar median CMAP ratio <0.6) was present in 52 patients. This was similar to the observations by Wang et al (82) though the reverse split hand index was not highlighted in their study. They found a negative correlation between reduction of CMAP and MRC grade of

abductor pollicis brevis (APB). In our study we found a statistically significant positive correlation between MRC sum score and ulnar median CMAP ratio of the affected limb ($r = 0.24$, $p = 0.045$). F wave latency prolongation of ulnar nerves was observed in 25 (35%) patients similar to the results observed by Huang et al (24).

EMG abnormalities were present uniformly in all patients with bilateral asymmetric pattern of involvement in 45 patients (63.3%). The subclinical involvement of the unaffected limb was also observed by Huang et al to a lesser extent (24). Denervation pattern was recorded from proximal cervical segments in 18%. Similar observation of the subclinical affliction of the proximal cervical segments have not been recorded in other studies. We also observed that paraspinal muscle involvement was present in 20 (28%) of our patients. Involvement of paraspinal muscles has not been well documented in the previous studies. The lack of florid involvement of paraspinal muscles despite HD being an anterior horn cell disease still remains unanswered.

Radiologic characteristics

MRI cervical spine flexion studies with contrast is the gold standard of diagnosis which was performed in 37(52.1%) patients of our cohort. Most of our patients were referred from outside centres with already available images without contrast. The most frequent abnormality encountered was the thinning of cord in 46 (65.7%) patients, more commonly in the lower cervical segments. In earlier studies, Pradhan and Gupta found focal cord atrophy in neutral neck position on MRI in 100% of their cases, while Hirayama and Tokumaru have reported this in only 50% of their cases (14,39,77). Among the imaging features discussed above, localized lower cervical cord atrophy, asymmetric cord flattening and loss of attachment have an accuracy of 80% in identification of the disease; loss of attachment has been proposed as the most valuable finding for diagnosing HD in the neutral position. (74, 98). Loss of cervical lordosis and hyperintensity of anterior horn cells was observed in 41% of our cases. We found a statistically significant correlation of thinning of cord with polyminimyoclonus ($r=0.3$, $p=0.009$).

MRI findings on cervical spine flexion like compression of the spinal cord by tight dura is thought to be one of the most important pathogenetic factor. In their study on seventy-three patients, Hirayama et al. found that dynamic compression of the lower cervical cord resulting

from forward displacement of the spinal cord and posterior cervical dural sac on neck flexion was limited to an early and progressing stage of the disease (39). Nevertheless, Pradhan and Gupta's study on 35 patients demonstrated that the posterior dura mater and spinal cord both move forward independently when stretched longitudinally, and that the cord compression was not caused by the dura mater's forward displacement (14,77). In our study we observed narrowing of spinal canal in 6% while the anterior displacement of dura was observed in 37% cases. Tashiro et al observed anterior displacement of dura with narrowing of anterior spinal canal in around 70-80% patients (20).

Contrast enhancement, crescent shaped hyperintense mass in posterior epidural space was observed in 29 (41%) cases in our patients. Preetish et al in his study also observed similar radiological findings (16). We observed a statistically significant association between disease course and contrast enhancement of venous plexus which remains unique to our study. Comparison of findings of our study with previously published studies are summarised in table 6.1 and 6.2.

Table 6.1 – Comparison with studies on clinical characteristics of patients with HD

	Gourie- Devi et al 2003(26)	Tashiro et al 2006(20)	Nalini et al 2014(66)	Preetish et al 2015(16)	Bo Zhou et al 2010(23)	Valerio et al 2013(97)	Our study
N	44	333	224	26	192	8	71
Mean age	19.8 (13-32)	17.6	19.5 ±4.1 (13 – 33)	20.9 ± 7	18.6(13- 28)	17.8	19.1±3.86
Male: Female ratio	10:1	281:34	9:1	All males	6.7:1	3:1	70:1
Disease progression	Static -7 (16%)	Slow progressio n -275 Rapid - 3	Static- 27(12.1%)	Static - 5(20%)	All slow progressor s	All low progressors	Static – 32 (45%) Slow progressors - 38(53.5%)
Laterality of symptom onset	Unilateral - 44(100%)	U-72%	U – 100%	Bilateral - 10(38.5%)	Unilateral -90%	b/l -2	U – 48(67.6%) B – 23 (32.3%)
Distribution of weakness* / wasting**	*Distal -19 (43.2%) Distal and proximal - 24(54.5%) Proximal - 1(1.4%)	*Proximal -26%	Proximal only -8(3.6) Proximal wasting – 42.8%	*Proximal -25 (13)	*Proximal -17.2%	*Prox -1	Distal –50 (70.4%) Both – 20 (30%) Proximal -1

Weakness on examination	Bilateral - 5(11.4%)	Bilateral asymmetric-24.8% B/l symmetric - 3.1%	Bilateral - 30%	B/l symmetric -10	b/l - 25(13%)	4	Bilateral - 45(63%) Asymmetric- 38(53.5%)
Initial symptom	--	--	--	--	--	--	Weakness - 53 (74.6%)
Cramps	7(15.9%)	--	35(15.6)	7(26.9%)	0	0	4(5.6%)
Sensory symptoms	--	--	51(22.8)	6(23%)	5.7%	2	10(14 %)
Fasciculations	21(47.7%)	101(30.3%)	--	24(92.3%)	39.1%	--	24(33.8%)
Cold paresis	12(27%)	205(61.5%)	116(51.8%)	16(61.5%)	156(81.3%)	--	14(19.7%)
Family history	No	2	No	No	1	No	2 (28.1%)
Proximal involvement	25(55%)	26%	108(48)	5(15.4%)	17.2%	1	21(30%)
Pattern of wasting	Bilateral -5	98%(laterality not mentioned)		b/l-10%	--	b/l -4	Bilateral -47 (66.2%)
Polyminimyclonus	28(81.8%)	221(66.3%)	34(15%)	26	149(77.6%)	--	48 (68%)
Deep tendon reflexes of UL- Brisk	4(9.1%)	127 (38.1%)- tendon reflex abnormalities	35(16%)	11(42.3%)	12(6.3%)	0	10 (14%)

Deep tendon reflexes of LL – Brisk	3(4.2%)		15.7%	14(53.8%)	--	0	19 (26.7%)
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Table 6.2 - Comparison with studies on electrophysiologic and radiological characteristics of patients with HD

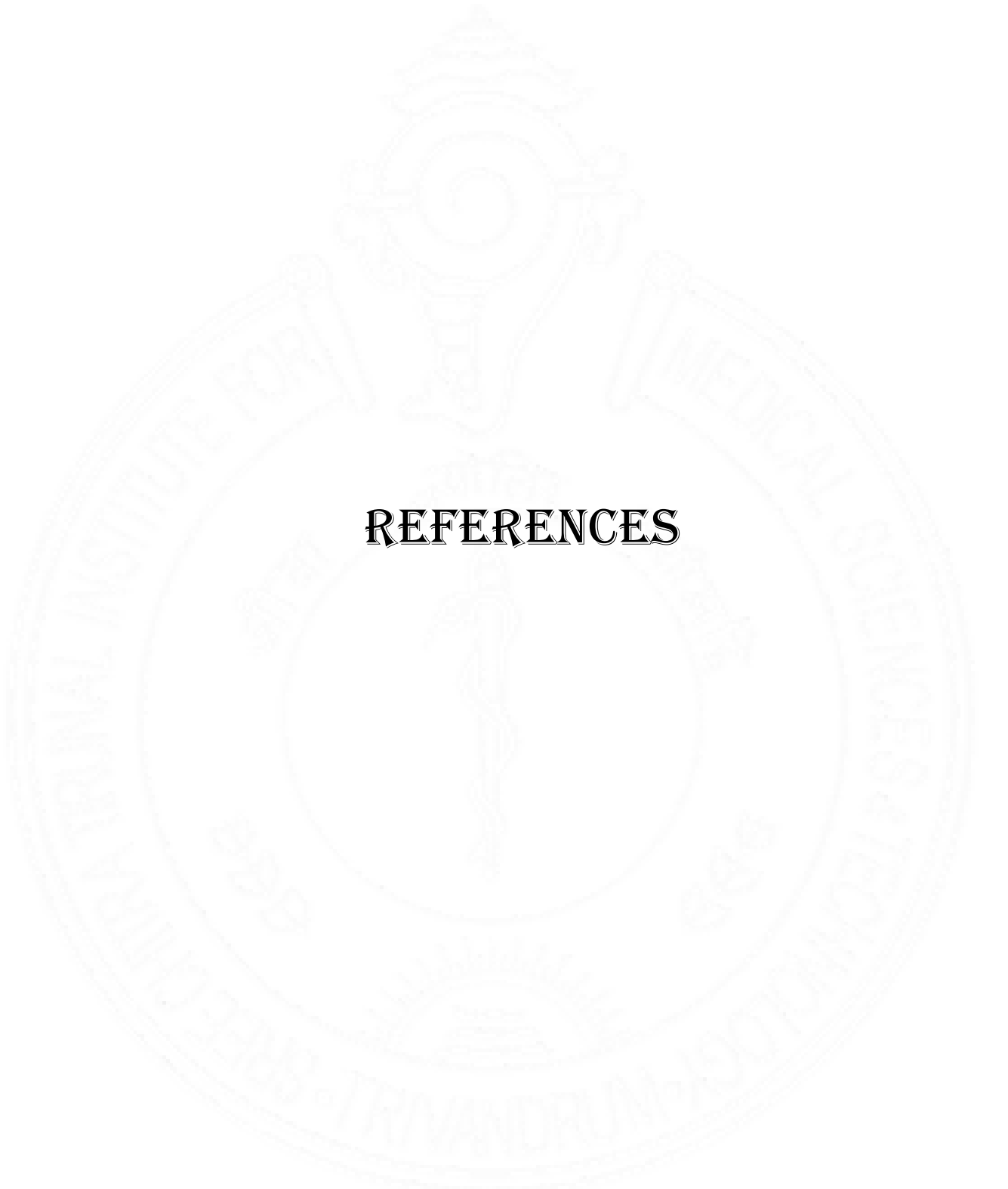
	Gourie Devi et al 2003	Tashiro et al 2006	Nalini et al 2014	Preetish et al 2015	Bo Zhou 2010	Our study
Nerve conduction study abnormalities	Normal 100%	EMG abn- 241(98.4)			Prolonged F - 25.5%	37(52.1%)
Pattern of EMG abnormalities Acute denervation	Affected limb -20 (45%) c/l limb – 5	73.7% unaffected limb	Affected – 71% c/l limb -21.1 denervation c/l limb-51%	Denervation-81.2%	c/l -95.8%, denervation LL- 3 cases	66(92.9)
Reinnervation pattern	Affected limb-100% c/l limb -7		Affected - 80.5% c/l limb – 85%	Affected - 60%	46(24%) Proximal- 25%	61(85.9)
MRI cervical spine with contrast – dynamic studies Yes No			89.2% MRI available MRI with contrast -9% - 51% abnormalities	24(92.3%)		34(48)
Loss of cervical lordosis			60.7%	15(57.7%)		41(58)
Thinning of cord		65%	44.6%	24(92.3%)	78(44.3%)	46(65)

Hyperintensity in anterior horn cells			16.1%	17(65.4%)	6	29(41)
Contrast enhancement (hyperintense signals/venous plexus)				20(83.3%)		29(41)
Prominent posterior epidural space		73%		7(26.9%)		
Crescent shaped epidural enhancement				20(83.3%)	112	29(41)
Anterior displacement of dura in flexion		68%	5.3%	19(86.4%)	127	26(37)
Narrowing of anterior spinal canal in flexion		81%	9%			6(8.4)
Cervical disc disease				11(42.3%)	14	19(27)

CONCLUSION

CONCLUSION

- The most common clinical presentation in our study cohort was bilateral asymmetric upper limb involvement.
- Polyminimyoclonus was the most frequently detected clinical examination finding in our cohort.
- Apart from the typical findings ascribed to this disease, we also observed proximal upper limb involvement, hypereflexia of the limbs along with two familial cases.
- The most frequent electrophysiological abnormality was the reduced CMAP in ulnar nerve.
- The electrophysiological correlate of the reversed split hand index was observed in 52(73.2%) patients.
- The most recurring radiological abnormality in our cohort was thinning of the cord.
- We observed a statistically significant association between disease course and contrast enhancement of venous plexus.



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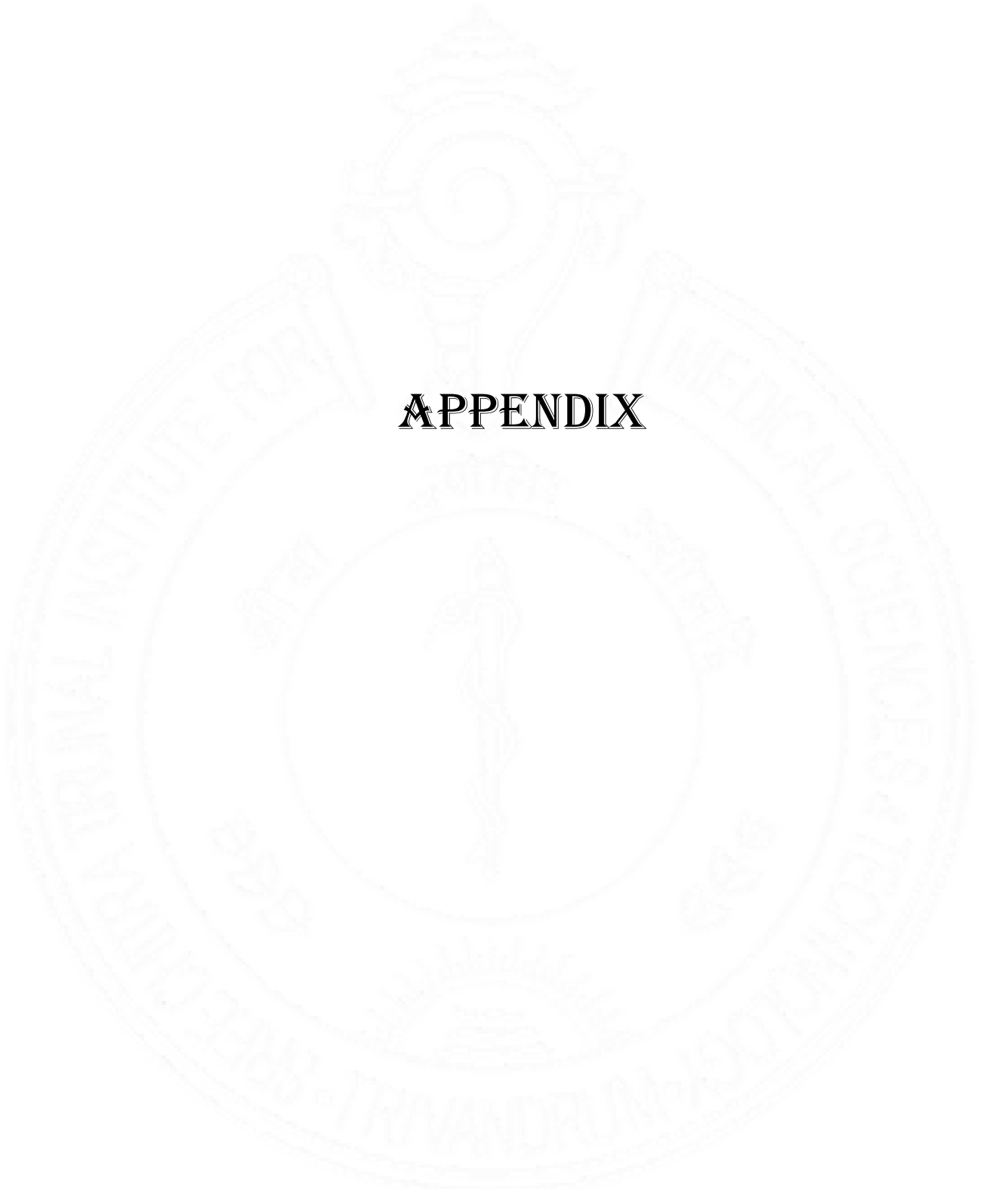
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APPENDIX

ABBREVIATIONS

AHC	Anterior horn cell
ALS	Amyotrophic lateral sclerosis
BMMA	Brachial monomelic amyotrophy
CMAP	Compound muscle action potential
EMG	Electromyography
HD	Hirayama disease
JASSMA	Juvenile asymmetric segmental spinal muscular atrophy
JMADUE	Juvenile muscular atrophy of the distal upper extremity
JNPMA	Juvenile nonprogressive monomelic amyotrophy
LOA	Loss of attachment
MMA	Monomelic amyotrophy
MRC	Modified Research Council
MRI	Magnetic resonance imaging
MUNE	Motor unit number estimate
MUNIX	Motor unit number index
NCS	Nerve conduction study
PBMA	Proximal bimelic amyotrophy
PDMA	Proximo-distal bimelic amyotrophy

CASE RECORD FORM

A. IDENTIFICATION INFORMATION

1	Date of recruitment									(DD/MM/YYYY)
2	Unique ID number									
3	Name									

B. DEMOGRAPHICS

1	Age			years
2	Sex	1. Male 2. Female 3. Other		

C. PERSONAL AND MEDICAL HISTORY

1	Smoking	Current Past Never
2	Alcohol intake	Current Past Never
3	Comorbidities	Diabetes Mellitus/Hypertension/ Cancer
		If yes, specify: _____
8	Spinal surgery	1. Yes 2. No If yes, specify: _____
9	Head or neck trauma	1. Yes 2. No If yes, specify: _____
10	Chronic infections	1. Yes 2. No If yes, specify: _____
11	Others	1. Yes 2. No If yes, specify: _____

A. DISEASE CHARACTERISTICS

1	Age at symptom onset			years				
2	Symptom onset							(MM/YYYY)
3	Time of diagnosis							(MM/YYYY)
4	Duration of illness (months)							
5	Time to nadir (months)							
6	Disease course	Static/ progressive						
7	Disease duration							
8	Last follow up							

B. SYMPTOMS AND SIGNS

1	Disease course	1. Progressive 2. Static
2	Symmetry	1. Symmetric 2. Asymmetric
3	Weakness at onset	1. Right 2. Left 3. Bilateral
4	Symptom at onset	
5	Pattern of weakness	
6	Distribution of weakness	
7	Pattern of wasting	1. Yes 2. No If yes, specify: _____
8	Distribution of wasting	
9	Tremors	
10	Cold paresis	
11	Neck pain	
12	Neck weakness	

13	Lower limb symptoms	1. Yes ☐ 2. No ☐ If yes, specify: _____
14	Sensory symptoms/signs	1. Yes 2. No
15	Pain limbs	1. Yes 2. No
16	Pattern of wasting	
17	Polyminimyoclonus	
18	Tone	
19	Medical Research Council Sum Score (MRCSS) – 80-point scale	
20	Reflexes	
21	Any other atypical feature	If yes, specify: __
22	Neck deformity	1. Yes ☐ 2. No ☐ If yes, specify: _____

C. INVESTIGATIONS

1	MRI cervical spine	
2	Flexion and extension films	
3	Contrast given	
4	Abnormalities in MRI cervical spine	1. Thinning of cord ☐ 2. Hyperintensity of anterior horn cells ☐ 3. High intensity mass in posterior epiduralspace ☐ 4. Anterior displacement of dura in flexion ☐ 5. Narrowing of anterior spinal space in flexion ☐ 6. Normal ☐
5	Other abnormalities	
6	Motor conduction studies	

7 8 9	Median CMAP Ulnar CMAP Radial CMAP	
10	Ulnar/Median CMAP ratio	
11	Sensory conduction studies	1. Normal 2. Abnormal
12	Electromyography	1. Neurogenic 2. Myopathic 3. Normal
13	If neurogenic EMG, sites of abnormality	1. Hand muscles right 2. Hand muscles left 3. Forearm muscles right 4. Forearm muscles left 5. Arm muscles right 6. Arm muscles left 7. Cervical paraspinal muscles 8. Thoracic paraspinal muscles 9. Lumbosacral paraspinal muscles Lower limb muscles
14	Any other abnormal investigation	1. Yes 2. No 10. If yes, specify: _____



श्री चित्रा तिरुनाल आयुर्विज्ञान और प्रौद्योगिकी संस्थान, त्रिवेन्द्रम
तिरुवनन्तपुरम - ६९५०११, केरल, इंडिया
SREE CHITRA TIRUNAL INSTITUTE FOR MEDICAL SCIENCES AND TECHNOLOGY, TRIVANDRUM
Thiruvananthapuram - 695 011, Kerala, India
(An Institute of National Importance under Govt. of India)

Grams : Chitramet, Phone : +91-471-2443152, Fax : +91-471-2550728 / 2446433, E-mail : sct@sctimst.ac.in, Website : www.sctimst.ac.in

Institutional Ethics Committee

(IEC Regn No. ECR/189/Inst/KL/2013/RR-21)

SCT/IEC/2097/AUGUST/2023

05.10.2023

Dr. Karthika Ajit V

Post Doctoral Fellow-Neuromuscular disorders

Department of Neurology

SCTIMST, Thiruvananthapuram

Dear Dr. Karthika Ajit,

The Institutional Ethics Committee held on 24th August, 2023, reviewed and discussed your application to conduct the study titled "CLINICO RADIOLOGICAL AND ELECTROPHYSIOLOGICAL PROFILE OF PATIENTS WITH HIRAYAMA DISEASE – RETROSPECTIVE STUDY " (IEC/2097).

Principal Investigator	Dr. Karthika Ajit V, Post Doctoral Fellow-Neuromuscular disorders, Department of Neurology, SCTIMST
Co-Principal Investigator(s)	Dr. Sruthi S Nair, Additional Professor, Department of Neurology, SCTIMST
Duration of the study	12 months

The following members of the Ethics Committee were present at the meeting held on 24th August, 2023

SL No.	Member Name	Highest Degree	Gender	Scientific /Non Scientific	Affiliation with Institution(s)
1	Dr. Kala Kesavan P	MBBS, MD	Female	Basic Medical Scientist	No
2	Smt. Sathi Nair	MA (English Literature)	Female	Lay Person	No
3	Adv. Priya Kaimal	LLM, MBL	Female	Legal Expert	No
4	Dr. P. Manickam	BSMS, MSc (Epid), PhD	Male	Health Science Expert/ Social Scientist	No
5	Dr. Christina George	MD Psychiatry	Female	Clinician	No
6	Dr. Manikandan S	MBBS, MD, PDCC	Male	Clinician	Yes
7	Dr. Syam K	MBBS, MD, DM	Male	Clinician	Yes
8	Dr. Srinivas G	PhD	Male	Basic Medical Scientist (Member Secretary)	Yes

The following documents were reviewed:

Original submission

- 1 Checklist Form
- 2 Covering letter addressed to the Chairperson, IEC, SCTIMST dated 07.06.2023
- 3 Covering letter addressed to the Chairperson, IEC, SCTIMST dated 07.06.2023 from Dr. Sruthi S Nair, Additional Professor, Department of Neurology, SCTIMST
- 4 IEC Application Form
- 5 Declaration form
- 6 Research Proposal
- 7 Case Record Form
- 8 CV of PI and Co-PI
- 9 SRC Recommendation Letter

Revised submission

- 1 Covering letter addressed to the Member Secretary, IEC, SCTIMST dated 04.10.2023
- 2 Responses/Amendments made based on the Reviewer's comments
- 3 Covering letter addressed to the Chairperson, IEC, SCTIMST dated 04.10.2023 from Dr. Sruthi S Nair, Additional Professor, Department of Neurology, SCTIMST
- 4 Checklist Form
- 5 Covering letter addressed to the Chairperson, IEC, SCTIMST dated 07.06.2023
- 6 Covering letter addressed to the Chairperson, IEC, SCTIMST dated 07.06.2023 from Dr. Sruthi S Nair, Additional Professor, Department of Neurology, SCTIMST
- 7 IEC Application Form
- 8 Declaration form
- 9 Research Proposal
- 10 Case Record Form
- 11 CV of PI and Co-PI

IEC Decision

The IEC approved the conduct of the study in the present form.

Remarks:

The Institutional Ethics Committee expects to be informed about the progress of the study, any SAE occurring in the course of the study, any changes in the protocol and patient information/informed consent and asks to be provided a copy of the final report.

There was no member of the study team who participated in voting / decision making process. The ethics committee is organized and operated according to the requirements of Good Clinical Practice and the requirements of the Indian Council of Medical Research (ICMR).

Sincerely,



Dr. G. Srinivas
Member Secretary IEC

MEMBER SECRETARY
INSTITUTIONAL ETHICS COMMITTEE (IEC)
SCTIMST, THIRUVANANTHAPURAM



