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Case Report

Novel reports of distal hereditary neuropathy due to mutations of SIGMAR 1 from India

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ABSTRACT

Distal hereditary neuropathies (dHMN) are hereditary neuromuscular disorders characterized by predominant distal motor neuropathy, leading to muscle atrophy, with a striking preservation of the sensory nervous system. While there is occasional overlap with Charcot-Marie-tooth disease (CMT) and familial amyotrophic lateral sclerosis (fALS), these conditions typically represent distinct entities with better prognosis. Numerous gene defects are associated with dHMN, and on-going research continues to unveil novel mutations. Among these, the mutation in the sigma non-opioid intracellular receptor 1 gene (SIGMAR1) has been identified across diverse populations. SIGMAR1 encodes a non-opioid endoplasmic reticulum protein present in both the central and peripheral nervous systems, playing a crucial role in neuronal survival and maintenance. Notably, SIGMAR1 gene mutations are linked to two distinct motor neuron disease phenotypes: fALS and dHMN. This signifies the broad impact of SIGMAR1 mutations on the neurogenetic landscape, contributing to the understanding of the complex interplay between genetic factors and motor neuron disorders. The continuous discovery of new mutations emphasizes the dynamic nature of research in this field, shedding light on the intricate mechanisms underlying these debilitating conditions.

Keywords: Nerve muscle diseases, Inherited neuropathy, Distal hereditary neuropathy

INTRODUCTION

In 1980, Harding and Thomas published their seminal thesis on a group of disorders now called the dHMN. They studied 34 patients who had a "peroneal muscular atrophy."[1] They noted that these patients resembled those with hereditary neuropathies, but with a striking sparing of the sensory nervous system. These diseases are the dHMN, also known as distal spinal muscular atrophy/ type 5 SMA.

They are similar to CMT disease, albeit bereft of sensory findings. Clinical features of this illness are the triad of distal weakness with atrophy, sparing of the sensory system, and foot deformities.[2] Since these diseases are extremely rare, precise statistics pertaining to their incidence and prevalence are lacking. These diseases usually present as predominantly motor neuropathy; however, variants show overlap with CMT.

As proposed by Rossor et al[2], the dHMN are characterised into various types based upon certain clinical features. Here describe clinical features of two of our patients who presented with classical features of a dHMN. They were both subject to genetic analysis by targeted gene sequencing.

SIGMAR1 is a non-opioid ER protein encoded by the SIGMAR 1 gene. The SIGMAR1 has a wide array of proposed functions like stress response, plasticity, synaptogenesis, and ion channel regulation.[4-6] It is found

in the central and peripheral nervous systems, particularly motor neurons[7]. SIGMAR 1 has been identified in various families across the world, like those of Japanese, Italian, Chinese, Hispanic, and Portuguese ancestry, thus we here present a case series of two patients with the SIGMAR1 mutation from India.[1,2] This is perhaps the first series of patients with this genetic mutation reported from India.

Table 1: Clinical feature of different types of dHMN.[2]

Types	Clinical features
Type 1	Juvenile-onset, distal weakness and wasting in lower limbs more than upper limbs, Brisk reflexes, soft cerebellar signs
Type2	Similar to type 1, but presents in adulthood
Type3	Slower progression than other 2 types
Type 4	Infantile onset with diaphragmatic weakness
Type 5	Begin in second decade of life with predominant upper-limb symptoms
Type 6	onset in infancy with severe axonal length-dependent weakness
Type7	early adulthood with facial and arm weakness, along with possible vocal cord palsy
X linked dHMN	In males with axonal length dependent weakness
dHMN and pyramidal features	Classical form with pyramidal weakness
Congenital distal spinal muscular atrophy	Classical presentation since birth, with vocal cord palsy, sensorineural hearing loss, and tongue fasciculation's with arthogryposis.

Table 2: Genetic defects and affected function.[3]

Genetic defects	Affected function
HSPB1, HSPB8, BSCL2	Protein misfolding
IGHMBP2, SETX, GARS	RNA metabolism
HSPB1, DYNC1H1, DCTN1	Axonal Transport
ATP7A and TRPV4	cation-channel dysfunction

CASE REPORT

Case 1

A 20-year-old boy from Beed, Maharashtra, from India, born of a third-degree consanguineous marriage presented with progressive weakness of lower limb, followed by upper limb, that was associated with thinning of the limbs. The disease was progressive over 10 years. Examination revealed bilateral foot drop, with distal predominant weakness of lower limbs and upper limbs. Wasting was noted. Deep tendon reflexes were absent. Sensory examination was normal. CPK levels were normal. EDx revealed reduced CMAP with preserved SNAP with normal latencies and velocities. Imaging of the spine was normal. Whole exome sequencing revealed a homozygous missense variant in exon 2 of the SIGMAR1 gene (chromosome 9) that results in the amino acid substitution of isoleucine for threonine at codon 109.

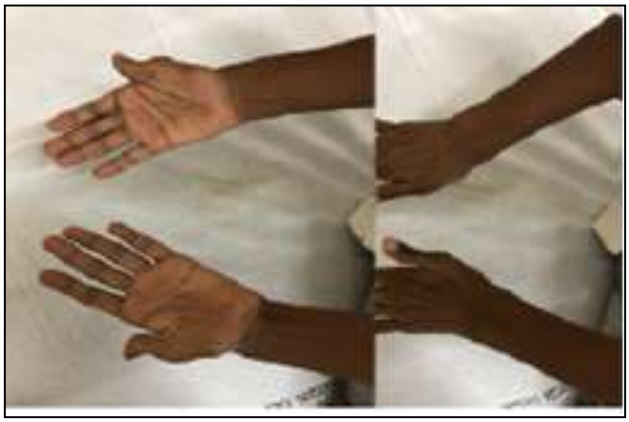

Figure 1: Atrophy of the small muscle of hand (Thenar, hypothenar, FDI).

Figure 2: Foot drop.

Case 2

A 13-year-old girl, from Faridabad, Uttar Pradesh India. Born of a non-consanguineous marriage, she presented to us with difficulty in walking since she was about 8 years of age. On examination, she had predominantly motor weakness, more prominent in the distal lower limb that was associated with wasting. She had developed ankle contractures. Sensory examination was normal. Her ankle jerks were absent; however, her knee jerks were brisk and she had an extensor plantar. Upper limbs were involved to a lesser extent; however, there was weakness and wasting more pronounced in the right distal muscles. She also had pes cavus. CPK levels were normal, and her NCS showed reduced CMAP with preserved SNAP. Velocities and

latencies were normal. She had predominantly lower motor neuron findings, with the odd extensor plantar and brisk knee jerk. This rare combination is found in ALS, although the disease progression was quite unlike even a familial ALS. Her clinical exome revealed a homozygous missense variant in exon 4 of the SIGMAR1 gene (chromosome 9) that results in the amino acid substitution of tryptophan for arginine at codon 175.

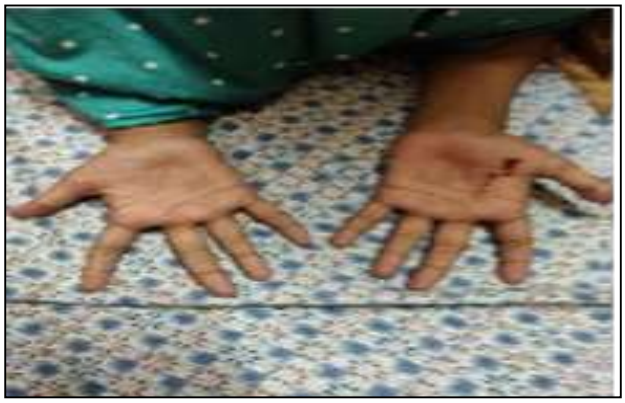

Figure 3: Atrophy of the small muscles of hand.

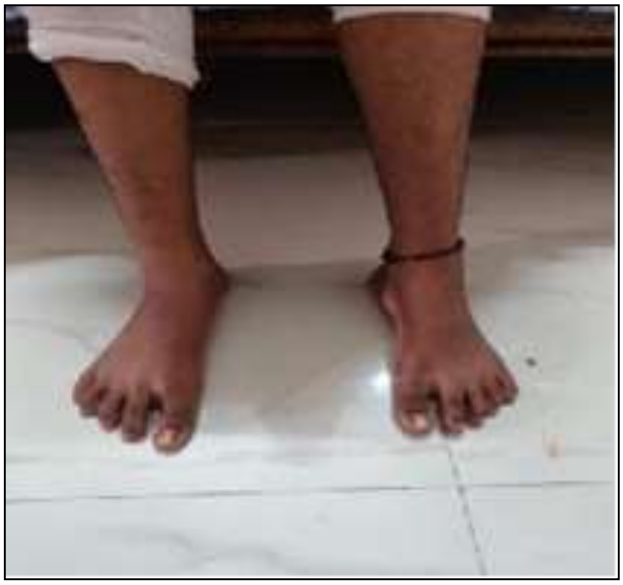

Figure 4: Atrophy of the distal limb with pes cavus.

Table 3: Comparison between two cases.

Case	Genotype	Protein	Ethnic origin	Age at onset (In years)	Distal weakness	Knee jerk	Ankle jerk	Babinski
Case 1	c.326C>T	p.Thr109lle	Indian	9-10	Present	Diminished	Diminished	Absent
Case 2	c.523C>T	p.Arg175Trp	Indian	6- 8	Present	Brisk	Brisk	Present

DISCUSSION

With the help of whole exome sequencing in our patients with pure motor distal weakness with spasticity we identified homozygous SIGMAR1 (c.326C>T, c.523C>T) mutation that present phenotypically as dHMN which is a rare variant based on online browsing tools.

The dHMNs are incredibly rare neurological diseases. Due to their rarity as well as their overlap with other inherited neuropathies and even motor neuron disease, they often go undiagnosed.

SIGMAR 1 mutation has been reported as presenting phenotypically as pure motor distal weakness along with associated pyramidal signs.[8-12] Only a handful of cases have been reported worldwide, and probably none from the India. The two patients reported here are from different parts of the country, from different communities. One patient is from Beed district of Maharashtra and the other from Faridabad district of Uttar Pradesh even they are from different sub-communities. Maxwell et al have reviewed 11 cases and have noted consanguinity in most of them contrary to that, our cases are non-consanguineous in nature.[13]

As per reported cases, the age of presentation is usually childhood which is similar to our cases, although cases at infancy and even old age (80 years) have been reported.[12,14] The pathology behind a late presentation of a SIGMAR mutation remains to be studied. Our patients presented with progressive, indolent distal motor weakness with atrophy owing to motor axonal neuropathy on nerve conduction studies and were similar to various published report on dHMN.[9,10,12]

Ververis et al have reviewed data from multiple studies and noted clinical features that include predominantly distal motor weakness with atrophy and upper motor neuron findings like positive babinski which is similar to our second patient. Hence, they can be misdiagnosed as having ALS. They too did note a few cases that had no pyramidal symptoms that is similar to our first case of pure motor distal lower limb weakness without pyramidal signs.[4] The phenotype of this patient seems to fit into the type 1 dHMN as described by Harding.[1]

Our reported cases seem to fit into autosomal recessive pattern which is similar to the inheritance pattern describe for SIGMAR 1.[4] Age of onset in early childhood was seen in our patients as well.[4]

A Horga et al proposed that SIGMAR1 manifest clinically with a combination of dHMN and pyramidal tract signs, with or without spasticity, in the lower limbs, and that preferential involvement of forearm extensors, but in both

of our case we did not find forearm extensor weakness, therefore further studies are needed to confirm forearm extensor weakness as a distinctive phenotype for SIGMAR1.[11]

To the best of our knowledge, this mutation is not yet reported from India. Our patients have a consistent clinical phenotype with the other cases reported.

With increased recognition of this entity and increased genetic testing, more families may be discovered with more preventive strategies in context to public health.

CONCLUSION

Our two patients probably represent the first reported cases of dHMN due to SIGMAR1 mutation from India. They present with similar clinical phenotype as those patients from cohorts around the world. dHMN due to SIGMAR1 mutation is an autosomal recessive disease that start in childhood and his slowly progressive. They usually have pyramidal signs as well, which often have them misdiagnosed as ALS. A few pointers towards an HMN and against ALS could be the indolent course, musculoskeletal abnormalities, and an often length-dependent type of motor weakness. It is important to identify this disease, as it may be confused with fALS, the prognosis of which is likely graver, while the prognosis of SIGMAR-1 dHMN seems to be relatively better than fALS. Often, patients diagnosed with "ALS" are not advised for genetic testing. Moreover, with further research, it is crucial to make an accurate diagnosis. Case 1 has been on follow up for 4 years his disease has worsened slightly with no change in mRS grade. Case 2 has been on follow up since 1 year. She feels the disease is progressing slowly although there is no change in mRS grade for her either. Further follow up is needed to ascertain the natural course of the illness.

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