Distal Spinal Muscular Atrophy

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Abstract
Spinal muscular atrophies (SMA) are clinically heterogenous group of motor system disorders characterised by progressive pure lower motor neuron involvement. The distal form of SMA is an extremely rare disorder, which presents in the adults and has a relatively slow progression with almost no effect on the patients’ life-span. Differential diagnosis of this syndrome include other forms of neuromuscular disorders with peroneal muscular atrophy like hereditary motor sensory neuropathy (HMSN) and distal myopathies, which need exclusion before confirming this rare entity. We present a young male with this disorder and briefly discuss the theoretical aspects.

INTRODUCTION
Spinal muscular atrophy (SMA) is a relatively infrequent group of motor system disorders with progressive pure lower motor neuron type of involvement characterized by proximal muscle weakness, atrophy, fasciculations and areflexia in varying combinations. The distal form of SMA is an extremely rare form of this disorder, which presents in the adults with predominantly distal muscle involvement in the lower limbs (Below-knee atrophy), which progresses to involve the upper limbs and has a relatively slow progression and almost normal life-span. Genetic involvement is well known with autosomal recessive and dominant inheritance being implicated and research is on to apply gene therapy in treating this otherwise untreatable entity. Other forms of neuromuscular disorders with peroneal muscular atrophy like hereditary motor sensory neuropathy (HMSN) and distal myopathies need exclusion before this rare entity is confirmed. Multi-speciality approach in rehabilitation and education to the parents helps in managing these patients and preventing this disorder by genetic counseling of the carriers.

CASE REPORT
A 22 years male, a right-handed engineering student, presented with insidious onset progressive weakness of all limbs of 4yrs duration. He was apparently well till 4yrs prior to admission when he developed progressive distal weakness with thinning of his legs and a high-stepping gait. Over the last two years, the weakness in his lower limbs progressed to involve the proximal muscles and he noted similar weakness and thinning of hand muscles. He had occasionally noted twitching of muscles in his arms and legs. He denied having stiffness of limbs, cramps, muscle pain, facial, bulbar, neck or trunk muscle weakness. There was no sensory or autonomic dysfunction. He denied any neck pain or constitutional symptoms. He was born out of a second-degree consanguineous marriage with normal developmental milestones. There was no similar case in the family.

On examination, he had normal vital parameters, neck : height ratio and there were no neurocutaneous markers. Neurological assessment revealed normal higher mental function, speech and cranial nerves. There was wasting of the intrinsic muscles of hands and feet, forearms and legs with relatively preserved proximal muscle groups. There was distal hypotonia, absolute areflexia, bilateral extensor plantar reflexes and a high stepping gait. There was no cerebellar, sensory or autonomic dysfunction. There was no abnormal spinal curvature or thickened nerves.

Investigations revealed a normal hematological and biochemical profile. Muscle enzymes levels, serum creatinine phosphokinase (104 IU/L), aspartate aminotransferase (49 IU/l) and lactate dehydrogenase (286 IU/l) were within normal limits. CSF studies for proteins and cellularity were normal. Nerve conduction velocity studies on the sensory and motor nerves of upper and lower limbs were within normal limits (Fig. 1). Electromyography studies revealed features of chronic denervation with reinervation in form of increased insertional and spontaneous activity and giant motor unit potentials (MUP) and incomplete recruitment (Fig. 2). Muscle biopsy was done which revealed extensive group atrophy and replacement of muscle fibres by fibrocollagenous tissue. Parents and siblings were not available for neurological assessment though it is planned at a later date.

DISCUSSION
Motor system disease is a group of disorders characterized...
by progressive degeneration of motor neurons in the spinal cord, brainstem and motor cortex. It presents with various combinations of upper and lower motor neuron involvement.

Progressive spinal muscular atrophy is a group of degenerative neuromuscular disorder characterized by pure lower motor neuron involvement with varying combinations of weakness, muscle wasting, areflexia and fasciculations which gradually involves the distal muscles of the lower limbs, upper limbs and variable neck, trunk and respiratory muscle involvement. A form of progressive spinal muscular atrophy with predominantly distal involvement is a rare subgroup of this disorder.\(^1,2\)

Distal SMA is an inherited form of SMA with autosomal recessive or dominant form of inheritance (Table 1). Autosomal recessive form is the more common form and occurs with a greater frequency in products of consanguineous marriages.\(^3,4\) It manifests as a very gradually progressive distal muscular weakness with slow clinical progression and almost normal life-span. Lower limbs are preferentially involved and below-knee atrophy with foot drop is commonly seen, as in our patient. Hands and arms are involved much later and to a lesser degree. However there is a type of distal SMA where upper limb predominance is seen (Type V).\(^5\) An Indian variant of this entity has also been described with predominant upper limb involvement.\(^6\) Carriers of the disease may be clinically normal though subtle EMG abnormalities may be the evidence of underlying abnormality.

Madras motor neuron disease (MMND) is a variant of SMA with unique geographic distribution to southern part of India and has the characteristic features of onset in the young, atrophy and weakness of the limbs, multiple cranial nerve palsies particularly the seventh, ninth to twelfth and sensorineural hearing loss.\(^7,8\)

Most important differential diagnosis of this peroneal muscular atrophy syndrome are peripheral neuropathies like HMSN (Charcot-Marie-Tooth II), where there is axonal type of involvement with almost normal conduction velocities. Chronic inflammatory demyelinating polyneuropathy (CIDP) and distal myopathies (Welander type) are other entities to be considered in the differential diagnosis.\(^5\)

Differentiation from HMSN is possible as there is always some degree of clinical or electrophysiological sensory nerve involvement in HMSN. Distal myopathies can be differentiated by presence of high CPK and LDH levels and EMG findigns of myopathy.

Muscle biopsy is conclusive evidence of the nature of muscular involvement. In neurogenic disorders, there is evidence of “group atrophy” with intervening muscle fibres normal or at times hypertrophic. In extreme forms of neurogenic atrophy, the muscle fibres may be replaced by fibrocollagenous tissue as in our patient.

The distal form of SMA has a relatively better prognosis compared to other forms of this disorder. Though the initial progression is rapid, the disease stabilizes in the later stages with patients remaining ambulant and having a normal life span. Since genetic inheritance is well known, genetic counseling of the carriers helps in preventing the disease.

**Table 1**: World Federation of Neurology Classification of Hereditary Motor Neuronopathies (Distal Spinal Muscular atrophy)\(^5\)

<table>
<thead>
<tr>
<th>Type</th>
<th>Inheritance</th>
<th>Age of onset</th>
<th>Age unable to walk</th>
<th>Life expectancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type I (Juvenile onset)</td>
<td>AD</td>
<td>2-20yr</td>
<td>Rare</td>
<td>Normal</td>
</tr>
<tr>
<td>Type II (Adult onset)</td>
<td>AD</td>
<td>20-40yr</td>
<td>Rare</td>
<td>Normal</td>
</tr>
<tr>
<td>Type III (Mild juvenile)</td>
<td>AR</td>
<td>2-10 yr</td>
<td>Rare</td>
<td>Normal</td>
</tr>
<tr>
<td>Type IV (Severe juvenile)</td>
<td>AR</td>
<td>4mths-20yr</td>
<td>30 yr</td>
<td>?</td>
</tr>
<tr>
<td>Type V (Upper limb predominance)</td>
<td>AD/</td>
<td>5-20 yr</td>
<td>Never</td>
<td>Normal</td>
</tr>
<tr>
<td>Type VI (Severe infantile)</td>
<td>AR</td>
<td>Infancy</td>
<td>Unable to walk</td>
<td>&lt;1yr</td>
</tr>
<tr>
<td>Type VII (With vocal cord palsy)</td>
<td>AD</td>
<td>10-20 yr</td>
<td>Rare</td>
<td>Normal</td>
</tr>
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</table>
There is no definitive therapeutic modality available. Management of this disorder involves active multi-specialty approach with neurologist, occupational and physical therapist and rehabilitation experts playing the major role. Respiratory support and care of the bed-ridden is seldom required in the natural course of distal SMA. Patient education about the natural course of the disease and its prognosis is important to involve the patient in the management process. Knowledge about the chromosomal involvement and recent advances in gene therapy can pave way for a possible genetic treatment for this untreatable entity.

In conclusion, distal SMA is an extremely rare form of motor system disease.

Commoner causes of similar presentation are other peroneo-muscular syndromes, which can be excluded by clinical, electrophysiological, and biochemical methods. Prognosis is relatively better than other forms of SMA. Patient education with multi-speciality approach to rehabilitate these patients is pertinent in managing these patients.

**REFERENCES**