Motor Neuron Disease with Descending Paralysis in a 55-Year-old African Man: A Review of the Pattern of Presentation

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DOI: https://dx.doi.org/10.47772/IJRISS.2023.7925

Received: 17 July 2023; Accepted: 17 August 2023; Published: 22 September 2023

ABSTRACT

Motor neuron diseases (MNDs) are neurodegenerative disorders that are distinguished by muscle wasting and loss of muscle strength following the gradual deterioration and death of Motor Neurons. Amyotrophic lateral sclerosis (ALS) is the commonest among MNDs.

These diseases are untreatable, with limited disease-modifying therapy options. There is a paucity of research on MNDs in Sub-Saharan Africa, particularly, molecular and genetic-based studies are deficient.

We present a case report of a 55-year-old African with a descending form of paralysis of Motor Neuron disease

Keywords: Motor-neuron disease-descending paralysis-pattern of presentation

INTRODUCTION

Motor Neuron diseases (MNDs) are fatal neurological diseases that are characterized by slow degeneration, and rapid muscular paralysis due to progressive loss of motor neuron[1]. The Major types are Amyotrophic lateral sclerosis (ALS), Primary lateral sclerosis (PLS), Spinal muscular atrophy (SMA), and progressive muscular atrophy (PMA)[1].

Amyotrophic Lateral Sclerosis has a prevalence of 4·9 –12 cases per 100,000 population[2] and an incidence of 3·1 cases per 100,000 person-years,[3] The two community-based surveys projected the disease prevalence rates of motor neuron disease to be 5/100,000 and 15/100,000 in Ethiopia and Nigeria, respectively[4] . Western Sub-Saharan Africa has a lower prevalence rate of 2.58-4.23 per 100, 000[5]. This shows ALS is a relatively rare disease[5]. However, there is an interplay of genetic, age-related, environmental, and developmental factors to have contributed to disease progression[6]. Though some MNDs are familial, others are sporadic[7]. In ALS, for example, there are both inherited and sporadic forms. Numerous genetic factors such as mutations in the C9orf72 and superoxide dismutase (SOD1) genes have been associated with familial ALS[7]. Also, Spinal Muscular Atrophy (SMA) is an autosomal recessive disorder with onset in infancy known as Werdnig-Hoffman disease, while SMA in childhood through to adulthood is known as Kugelberg Welander syndrome[7].

The different patterns of neuropathic (PN) disorders can be confusing to the clinician who is encountering them for the first time, but several key models of involvement can help lead to the proper diagnosis (Table

1). For the full category of neuropathic patterns, the "Pattern-recognition approach to neuropathy and neuronopathy has been described[8]. Some of the patterns of muscle weakness have also been documented (Table 2). The Pattern of Neuropathy seen in ALS is PN5[8]. The myopathy in pattern 6 (MP6; neck extensor weakness) and MP7 (tongue, pharyngeal, or diaphragm), are also present as an overlap syndrome in motor neuron disease (table 2)[9]. Typically, there are both upper motor neuron and lower motor neuron signs along with electro-diagnostic studies which are indicative of ALS[1].

Table 1. Clinical Patterns of Neuropathic Disorders (PN)[8]

Pattern	**Weakness**				**Sensory symptoms**	**Severe proprioceptive loss**
	Prox	**Dis**	**Asymm**	**Symm**		
Pattern 1– Symmetric prox & Distal weakness w/sensor y loss	+	+		+	+	
Pattern 2 – Distal sensory loss with/without weakness		+		+	+	
Pattern 3 – Distal weakness with sensory loss		+	+		+	
Pattern 4 – Asymmetric prox & distal weakness w/sensory loss	+	+	+		+	
Pattern 5 – Asymmetric distal weakness w/out sensory loss		+	+			
Pattern 6 – Symmetric sensory loss & upper motor neuron signs		+		+	+	+
Pattern 7* Symmetric weakness without sensory loss	+/-	+		+		
Pattern 8* Focal midline proximal symmetric weakness	+ Neck/extensor + Bulbar			+ +		
Pattern 9 – Asymmetric proprioceptive loss w/out weakness			+		+	+
Pattern 10 – Autonomic dysfunction						

Table 2. Clinical myopathy pattern (MP) of various Muscle disorders[9].

PATTERN	**CLINICAL PRESENTATION**
Pattern1.(MP1)	Proximal "Limb-Girdle" Weakness, weakness affecting predominantly the proximal muscles of the legs and arms, or the so-called "limb-girdle" distribution, eg most hereditary and acquired myopathies

ISSN No. 2454-6186 | DOI: 10.47772/IJRISS |Volume VII Issue VIII August 2023

Pattern 2.(MP2)	Distal Weakness of the upper or lower extremities, mostly symmetrical and more common features of neuropathies
Pattern3.(MP3)	Proximal Arm/Distal Leg Weakness (Scapuloperoneal). Weakness can be very asymmetric and sometimes involves the face eg Facioscapulohumeral Muscular Dystrophy, acid maltase deficiency, congenital myopathies, and Emery-Dreifuss dystrophy.
Pattern 4.(MP4)	Distal Arm/Proximal Leg Weakness eg myotonic dystrophy, In addition, the weakness is often asymmetric between the two sides eg, including body myositis
Pattern 5.(MP5)	Ptosis With or Without Ophthalmoparesis, predominant involvement of ocular and/or pharyngeal muscles. (without Ophthalmoparesis eg, Congenital myopathies, Nemaline myopathy, Central core myopathy, Desmin (myofibrillary) myopathy. With Ophthalmoparesis(Centronuclear myopathy Mitochondrial myopathy Multicore Disease Oculopharyngeal muscular dystrophy Oculopharyngodistal myopathy Neuromuscular junction disease (Myasthenia Gravis, Lambert-Eaton, Botulism), Myotonic dystrophy.
Pattern 6.(MP6)	Prominent Neck Extensor Weakness, common in two other neuromuscular diseases: amyotrophic lateral sclerosis and myasthenia gravis. Others eg. Isolated neck extensor myopathy (INEM)
	Dermatomyositis
	Polymyositis
	Inclusion body myositis
	Carnitine deficiency
	Facioscapulohumeral dystrophy
	Myotonic dystrophy
	Congenital myopathy
	Hyperparathyroidism
Pattern 7. (MP7)	Bulbar Weakness eg. Neuromuscular junction disorders such as myasthenia gravis and Lambert-Eaton myasthenic syndrome also frequently have bulbar symptoms and signs. This pattern is considered an “overlap” pattern with amyotrophic lateral sclerosis and other motor neuron disorders which can have significant bulbar involvement.
Pattern 8. (MP8)	Episodic Pain, Weakness, and Myoglobinuria **Related to exercise** “Couch Potato” syndrome Glycogenoses (McArdle’s, etc.) Lipid disorders (CPT deficiency) **Not related to exercise** Central non-neuromuscular causes: Neuroleptic malignant syndrome Status epilepticus

	Drugs/toxins Malignant hyperthermia Polymyositis/Dermatomyositis (rarely) Viral/bacterial infections
Pattern 9. (MP 9)	Episodic Weakness Delayed or Unrelated to Exercise eg □ Periodic paralysis Ca^{++} channelopathies (hypokalemic) Na^{++} channelopathies (hyperkalemic) Andersen-Tawil syndrome Secondary PP (thyrotoxicosis) □ Other: Neuromuscular junction diseases

Pattern 10. (MP 10)	• Improves with exercise
	  • Myotonia – Na^{++} or Cl^{-} channelopathy
	• Worsens with exercise/cold sensitivity
	  • Paramyotonia – Na^{++} channelopathy
	  • Brody's disease
	• With fixed weakness
	  • Myotonic dystrophy (DM 1)
	  • Proximal myotonic myopathy (DM 2)
	  • Becker's disease (AR Cl^{-} channelopathy)
	• Other:
	• Malignant hyperthermia
	• Neuromyotonia
	• Rippling muscle
	• Stiff-person syndrome

Findings have shown that sensory pathways of SOD1 transgenic mice, the most commonly used murine model of ALS, demonstrated pathological changes in the axons of the dorsal columns, the dorsal horn of the spinal cord, and dorsal root, and in the soma of the Dorsal Root Ganglia neurons as shown in figure 1[21].

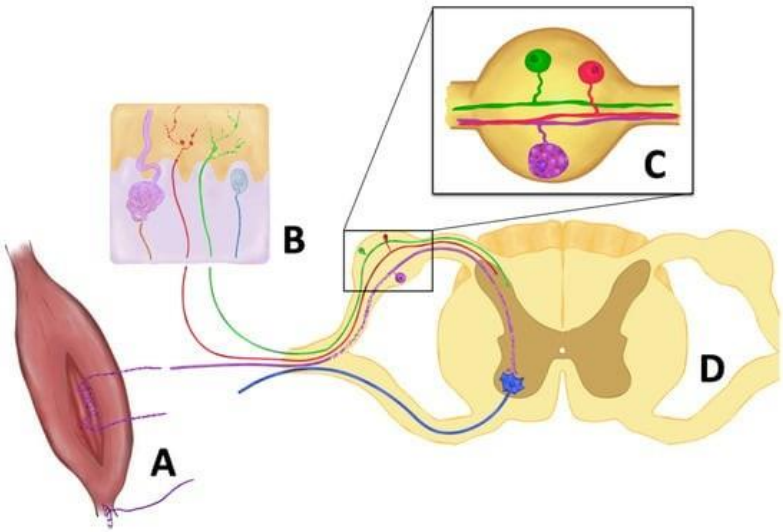

Figure 1. Main pathological changes in sensory afferents in ALS[21]. (**A**) Degeneration of type Ia and II sensory fibers innervating muscle spindles, while type Ib fibers (Golgi tendon organ) are preserved. (**B**). Reduction of intraepidermal nerve fibers, terminals of both peptidergic (red) and non-peptidergic (green) axons, with focal swellings. Meissner corpuscle innervation (blue) is also impaired, as well as sympathetic fibers innervating sweat glands (brown). (**C**) In the dorsal root ganglion, neuronal bodies are preserved, although vacuolization and accumulation of misfolded SOD1 protein are seen in proprioceptive neurons (purple). (**D**) In the dorsal root, larger axons show Wallerian degeneration. In addition, proprioceptive synapses in the anterior horn are reduced in certain animal models ($SOD1^{G93A}$ mouse) but preserved in others ($TDP43^{A315T}$ mouse)[21].

In the $SOD1^{G93A}$ mouse, a loss of small fibers has been seen in the skin, also at the level of sensory axons in the dermis and involving Meissner corpuscles, with evidence of retrograde sensory axonal loss as shownin figure 2[21].

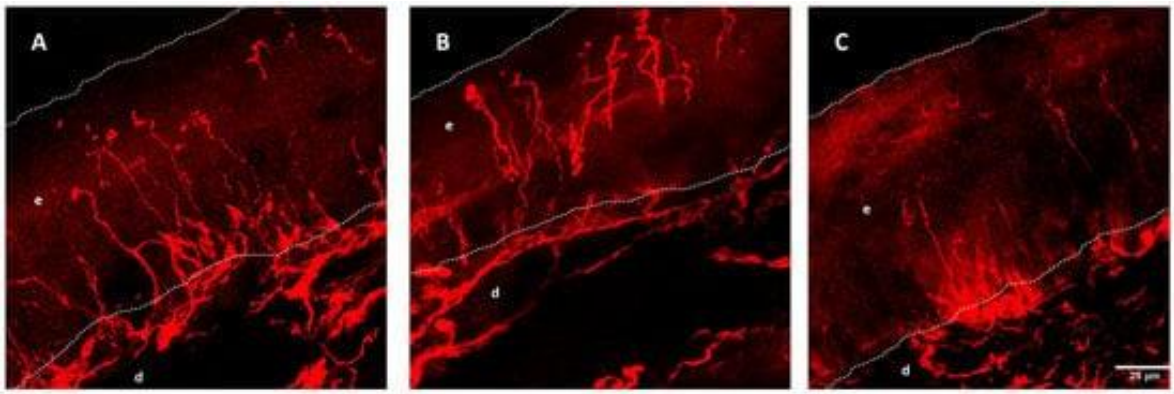

Figure 2. Intraepidermal nerve fiber (IENF)[21] density from wild-type (**A**), $SOD1^{G93A}$ mice of 8 (**B**), and 16 weeks (**C**). Dotted lines mark the limits of the epidermis (e) and dermis (d). IENF fibers are marked with PGP9.5 and show a decrease over time in the $SOD1^{G93A}$ mouse[21].

Motor Neurone diseases are incurable, with limited disease-modifying treatment options[10]. The approved drug by the Food and Drug Administration of the USA for the Management of ALS is riluzole, which delays the progression of the disease, and dextromethorphan/quinidine which offers symptomatic relief for pseudobulbar affect (inappropriate bouts of laughter or crying)[12].

CASE REPORT

A 55-year-old man presented with complaints of progressive weakness of the limbs for 6 years. He was in his usual state of health until 6 years ago when he noticed descending weakness which started with the right upper limb. Weakness was initially limited to the fingers, as he found it difficult to grasp objects and open doors, and has evolved to the weakness of the left upper limb in a space of a year. He has also witnessed the involvement of the right and left lower limbs in the last 4years. Weakness later spread to involve both proximal and distal regions, which include associated difficulty with raising the upper arm above the head and difficulty combing his hair. There were associated fasciculations, especially on both thigh regions. There was associated dysarthria and dysphagia without odynophagia with occasional nasal regurgitation, which worsened over the last 2 years for which had a procedure to enable him to feed through a tube in the stomach. Recently, there has been a frequent display of emotional outbursts in the form of crying or laughing in unwarranted circumstances. No associated tingling sensation, numbness, or pain on any part of the body. There was no sphincter dysfunction or visual loss, vertigo, frequent vomiting, or hiccups. He is not known hypertensive or diagnosed with Diabetes Mellitus. No history of previous stroke or Transient Ischemic Attack. There was no history of ptosis, diplopia, and undue fatigue. He had no antecedent history of headache, photophobia, and loss of consciousness. No history of cough, hemoptysis, or significant weight loss. He had no previous recurrent mouth ulcers, oral thrush, chronic diarrhea, or febrile illness. His

ISSN No. 2454-6186 | DOI: 10.47772/IJRISS |Volume VII Issue VIII August 2023

Retroviral Status was negative. No features were suggestive of connective tissue disease or autoimmune disorders. There was no associated history of prostatism; Frequency, urgency, strangury, incomplete voiding, hesitancy, or forking of the urine. There was no change in the color of urine on standing or abdominal pain. No history was suggestive of exposure to cyanide, lead, or organophosphate poison. No history of trauma to the back. No family history of similar symptoms; father, mother, siblings, or grandparents. He was not aware of his immunization history and there was no treatment for polio in childhood. No previous history of blood transfusion and surgery. He neither smokes nor takes alcoholic beverages and other psychoactive substances. No history of drug allergy.

He is a conscious middle-aged man, with no signs of meningeal irritation. His pupils were 3 mm, round and symmetrical, and bilaterally reactive to light and accommodation. The Motor examination showed: the presence of spontaneous and induced fasciculations. There was significantly reduced muscle bulk with wasting of the Right Upper Limbs and Left Upper Limb muscles more than the lower limb muscles. This was worse distally. The Power on the Right and Left upper limbs was 3/5 while the Right and Left lower limbs were 4/5. There were Hypertonia, Hyperreflexia globally and plantar reflexes also were extensor bilaterally. No sensory abnormalities detected: fine touch, pain, and temperature intact. The proprioception, and vibration senses were intact and there was no sensory level.

A cardiovascular system examination showed that the pulse rate was 72 beats per minute and the Blood pressure was normal at 127/70 mmHg. The Chest and Abdominal examinations were essentially normal with the presence of a Percutaneous Endoscopic Gastrostomy tube secured through the abdominal wall.

Nerve Conduction Study: The F- wave was not present in the right and left median and ulnar nerves but normal latency was noted in the other nerves tested. The Tibial H reflex was normal bilaterally. The nerve conduction study suggests severe axonopathy of the right median and ulnar nerve with impairment of proximal conduction (absent F wave). There was also evidence of early axonopathy in the right and left common peroneal and tibial nerves respectively.

Electromyography (Emg) Study: Needle EMG was normal in the lower limb muscle tested. There were fibrillation potentials and positive sharp waves in the right and left bicep muscle with high amplitude, long duration motor unit action potential (MUAP) with reduced recruitments suggestive of chronic denervation with reinnervation. The right and left Abductor Polllicis Brevis (APB) and Abductor Digiti Minimi(ADM) muscles showed fasciculations with no demonstrable MUAP.

Cervical MRI, Electrolyte, Urea and Creatinine, Full blood count, PSA, ESR, Manteaux, and Lipid profile were not remarkable. Genetic studies were not available in our environment.

Conclusion:

Severe motor axonopathy with features of chronic denervation-reinnervation in the Upper Limbs. Early motor axonopathy in the lower limbs. The most likely diagnosis is **Motor Neuron Disease (MND)** with **Amyotrophic lateral sclerosis variant/subtype.**

The patient and relatives were subsequently counseled on diagnosis and likely treatment outcome. They were properly informed about the need for physiotherapy and Hospice care. He was placed on tablet Riluzole 50 mg twice daily, tablet Tocovid 50 mg twice daily, and regular follow-up visits.

Ethical Issues/Consideration:

Ethical permission to conduct this research was gotten from the Research and Ethics Committee of the hospital. The code of ethics aimed at protecting the rights of the patient used as the subject of the research was upheld. No harm or discomfort to the participant was allowed. Privacy and confidentiality were

endorsed. No Financial obligation to the patient.

DISCUSSION

Motor Neuron Diseases (MNDs) are fatal, neurodegenerative diseases especially Amyotrophic lateral Sclerosis (ALS) [11]. The clinical manifestations of ALS include muscle weakness, limb paralysis, and bulbar and corticobulbar symptomatology (e.g., dysphagia, dysarthria, tongue wasting) due to the progressive degeneration of upper and lower motor neurons[11]. In ALS, the seriousness of the symptoms worsens rapidly over time. Indeed, it has been predicted that about half of patients with the disease die within the first 3-years after diagnosis, commonly from respiratory complications[11].

Our patient presented with a Clinical Pattern of Neuropathic Disorders 5(PN5) [table1] overlapping with clinical myopathy 7(table 2). This is asymmetric distal weakness and later proximal involvement without sensory loss in a descending fashion with features of upper and lower motor neuron lesion characteristically NP5 pattern spreading to involve muscle weakness affecting bulbar region MP7 of a clinical pattern of myopathy, which is in keeping with Amyotrophic lateral sclerosis(ALS)[8].

Patterns of Neuropathy/ Weakness

Neuropathic disorders can be generally divided into disorders affecting the peripheral nerve processes (neuropathy) or nerve cell body (neuronopathy). This can be inherited or acquired, and have diverse clinical courses[8]. Motor neuron diseases are neuronopathies. When assessing patients with suspected neuropathies or neuronopathies several key questions can help you further classify these disorders:

- What portions of the nervous system are affected: Is it motor, sensory, autonomic, or combinations of more than 1 system? [8] Our patient presented with motor neuron disorder in a descending fashion with no sensory or autonomic manifestation.
- Where is the muscle weakness (proximal, distal, or both) and is it symmetric or asymmetric? [12] We discovered our patient had asymmetric, distal, and later proximal weakness affecting the upper and lower limbs.
- If there is sensory involvement is there pain, or proprioceptive loss? [12] There was none in the index patient.
- Over what period did symptoms evolve: acute (< 4 weeks), subacute (4-8 weeks), or chronic? [12]. Our patient presented very late(chronically progressive).
- Is there a family history of a similar disorder? [12]. There was no family history of similar illness in the index case and no facility to run genetic studies.

MNDs are classically motor syndromes (sensory sparing) that show subtle onset[12], are chronically progressive, can be distal, proximal, or mixed, and can have diverse combinations of upper and lower motor neuron findings. They can be inherited or sporadic[12]. There are several neuropathic patterns seen in the MNDs.

1. Asymmetric distal weakness without sensory loss (NP5)
2. Symmetric weakness without a sensory loss (NP7)
3. Focal midline proximal symmetric (NP8)

Amyotrophic Lateral Sclerosis (ALS)

ALS is an advancing disorder of motor neurons in the brain and spinal cord that is always fatal. It can manifest with equal or various frequencies as NP 5 in the arms, NP of the legs, or bulbar NP8/MP7 onset[12]. Clinically patients have mixed upper and lower motor neuron findings on examination. The bulk of patients

have sporadic disease (~85%). ALS is essentially a clinical diagnosis, sustained by neuro-physiological testing. There are no remedies for ALS – but there are evidence-based strategies for standards of treatment.

A recent survey of ALS patients found that 85% had focal onset in one body segment, which progressed to the contralateral side and then to adjacent anatomical segments[13]. Clinical weakness spreads contra-laterally and rostrally or caudally, most often in an anatomically contiguous manner[14] as seen in our patient. Disease spread to non-contiguous segments was less common[14]. ALS presents numerous phenotypes. Bulbar onset and spinal (cervical, lumbar) onset ALS are the most common presentations unlike our patient, each constituting about a quarter to a third of cases, with less frequent manifestations of flail arm and leg, primary lateral sclerosis, progressive muscular atrophy, respiratory onset, and hemiplegic presentations[15,16]. Age, sex, and genetics contribute to ALS phenotypes. Older female patients may more commonly develop bulbar onset ALS, younger males classical ALS, younger males and females pure UMN diseases, males flail arm variant, older males flail leg variant and respiratory onset[17]. Some genetic mutations favor certain phenotypes. One recent study suggests that phenotypes may vary globally[18]. German ALS patients have an older onset age (66.6 years), a larger proportion of bulbar onset (35.9%), and a smaller male-to-female ratio (1.33) versus Chinese patients (53.2 years onset age, 22.8% bulbar, 1.51 male-to-female ratio)[18]. In another study, a 61-year-old black African man who worked as a trauma nurse was diagnosed with Motor neuron disease(ALS) presenting with acute hypercapnic respiratory failure[19] as the only symptom.

Patterns of descending versus ascending spread in ALS[20]

Bulbar UMN onset progressed faster than bulbar LMN onset ($P < 0.0025$)[20], which may be the reason for the very slow progression in our patient. Both bulbar UMN onset and bulbar LMN-onset patients progressed more to the upper limbs than to the lower limbs ($P < 0.0025$).

Upper limbs UMN- and LMN-onset syndromes were more likely to progress to lower limbs than to the bulbar region ($P < 0.0025$), similar to our patient, but rostral-caudal progression was faster in upper limbs UMN onset than upper limbs LMN-onset disease ($P < 0.0025$) in contrast to our patient progression.

Although caudal-rostral progression was similar for both upper limbs UMN and LMN onset ($P = 1.0$)[20]. Lower limbs UMN-onset disease progressed more frequently to upper limbs and bulbar regions than LMN onset ($P < 0.0025$ to both bulbar and upper limbs), however, our patient had upper limb UMN onset disease. But the speed of spread to those regions was similar for both lower limbs LMN and UMN onset (to bulbar $P = 1.0$: to upper limbs $P = 0.363$)[20] and for both groups was faster to upper limbs than to bulbar region (lower limbs UMN onset, $P < 0.0025$ and lower limbs LMN onset, $P < 0.0025$).

In general, lower limbs LMN onset progressed more by anatomical contiguity than lower limbs UMN onset (lower limbs UMN onset to upper limbs *vs.* bulbar, $P = 1.0$: lower limbs LMN onset to upper limbs *vs.* bulbar, $P < 0.0025$)[20].

CONCLUSIONS

ALS remains difficult to diagnose and manage. This is due to heterogeneous ALS presentation and phenotype, and symptom and sign overlap with other illnesses. They have different patterns of descending/ascending paralysis and rate of spread. Earlier on in the diagnostic process, physicians should refer patients presenting with progressive dysarthria, dysphagia, limb weakness, or respiratory failure for proper management.

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