ISSN:0975-1459
Journal of Pharmaceutical Sciences and Research
www.jpsr.pharmainfo.in

Lower Motor Neuron Diseases: An Indepth Review

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Abstract:
Motor neuron diseases (MND) are a group of neurological conditions that result in loss of nerve function over a period of time. They are broadly classified as Upper Motor Neuron Disease (UMND) and Lower Motor Neuron Disease (LMND). Lower motor neuron disease are those groups of MNDs that arise from the distal motor nerve in the anterior horn cell. Recent advances in the field of medicine has led to identify the involvement of genetic mutations in the pathophysiology of the MNDs. It has also aided in nurturing various management techniques. The current review will broadly describe the different types of Lower Motor Neuron Diseases prevelant and the current evolution in the managing of the patient with these conditions.

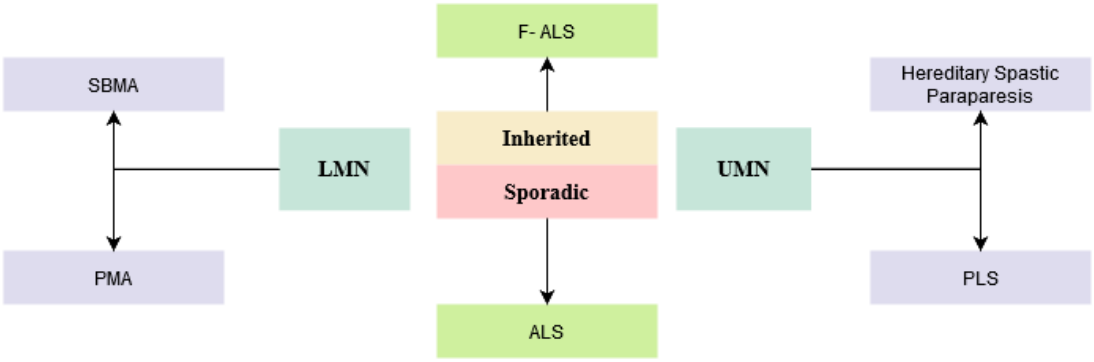
Keywords: UMND- Upper motor neuron disease, LMND- Lower motor neuron disease, SBMA- Spinal and Muscular Atrophy, SMA- Spinal Muscular Atrophy, dHMN- Distal Hereditary Motor Neuropathy, PMA- Progressive Muscular Atrophy, MMA- Monomelic Amyotrophy, PPS- Post-Polio Syndrome, GBS- Guillain- Barre Syndrome

INTRODUCTION:

Motor neuron diseases (MND) are gradually developing disorders of unknown origin which results in degeneration of motor neurons in cranial nerves nuclei, spinal cord and pyramidal neurons in the motor cortex [1]. It becomes clinically apparent during middle ages and is more common in men [2]. 5-10% of the cases are of familial origin and of these, 20% is caused by mutation of Superoxide dismutase (SOD1) gene [1]. The usual investigations done are: Electromyography (EMG), Sensory and motor nerve conduction studies, spinal imaging, brain imaging, CSF examination, etc [1]. The current review paper discusses elaborately on prevalent Lower motor neuron diseases and their advancing managing techniques.

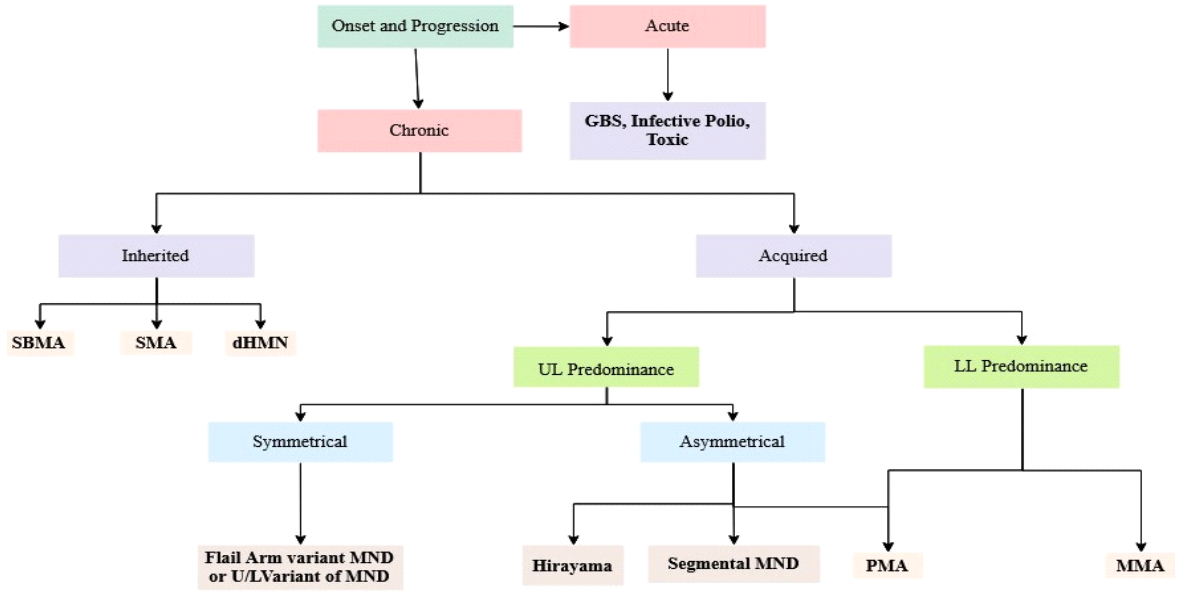
Classification of Motor Neuron Diseases:

Motor neuron diseases are broadly classified into: Upper Motor Neuron disease (UMND) and Lower Motor Neuron disease (LMND). In the case of UMND, the patient becomes hyper-responsive to stretching. They also present with flexion withdrawal, spasm, etc. The UMN lesion is more pronounced in the extensors of lower limbs and the flexors of upper limbs, brisk tensor reflexes, etc. In the case of LMN lesions, a loss of contraction develops resulting in weakness and reduced muscle tonicity. Following this, atrophy of muscles causes muscle wasting and depolarisation resulting in fibrillation, which can be detected by electromyogram [1].



LMN- Lower motor Neuron; UMN- Upper Motor Neuron; ALS- Amyotrophic Lateral sclerosis, F-ALS- Familial Amyotrophic Lateral Sclerosis; PLS- Progressive lateral Sclerosis; PMA- Progressive Muscular Atrophy; SBMA- Spinal and Bulbar muscular Atrophy

Figure 01: Spectrum of Motor Neuron Diseases, according to Statland et.al, 2015 [3]



GBS- Guillain Barre Syndrome; SBMA- Spinal and Bulbar Muscular Atrophy; dHMN- Distal hereditary motor neuropathy; MMA- Monomelic Amyotrophy; PMA- Progressive muscular atrophy; LL Predominance- Lower limb; UL - Upper limb; MND- Motor Neuron Disease

Figure 02: Diagnostic Algorithm proposed by Garg et.al, 2016 for LMN [4]

A. Heritable Lower motor neuron diseases:

1. Spinal and Bulbar Muscular atrophy (Kennedy's Disease):

Kennedy's disease is also known as Spinal and bulbar muscular atrophy (SBMA). Kennedy et al, in 1968, described spinal and bulbar muscular atrophy, in 11 patients taking notice of its X-link recessive pattern. Harding et.al, in 1982, reclassified it as X-linked bulbo-spinal neuronopathy. It occurs between the 3rd -5th decades of life. The disease is found to mainly involve the male population and minority of the females are carriers and asymptomatic women are involved in transmission of the disease. This is because of low level of androgen circulation and the Androgen Receptor stimulation in females [5]. In a cross-sectional study by Fratta et.al, 2014 in UK, it was stated that 61 cases of spinal bulbar and muscular atrophy have been identified in the past decade [6].

Gene mutation:

It is caused by the mutation of trinucleotide repeat in the Androgen Receptor (AR) gene. An expanded trinucleotide repeat of more than 37 glutamine proteins is sought to be responsible for the disease [5].

Pathophysiology:

The exact pathogenesis of Kennedy's disease remains unknown. Intranuclear inclusions consisting of misfolded polyglutamine-expanded proteins in affected neuronal populations is evident. The polyglutamine aggregation is followed by nuclear inclusion and impairment of function. It occurs as a result of transcriptional dysregulation and other mechanisms. The endocrine manifestations like gynaecomastia, reduced fertility, weakness and muscle atrophy occur due to loss of function mechanisms [5].

Clinical features:

On examination muscle atrophy, decreased, or absent tendon reflexes, tremor, cramping and fasciculations are observed [4,5,7].

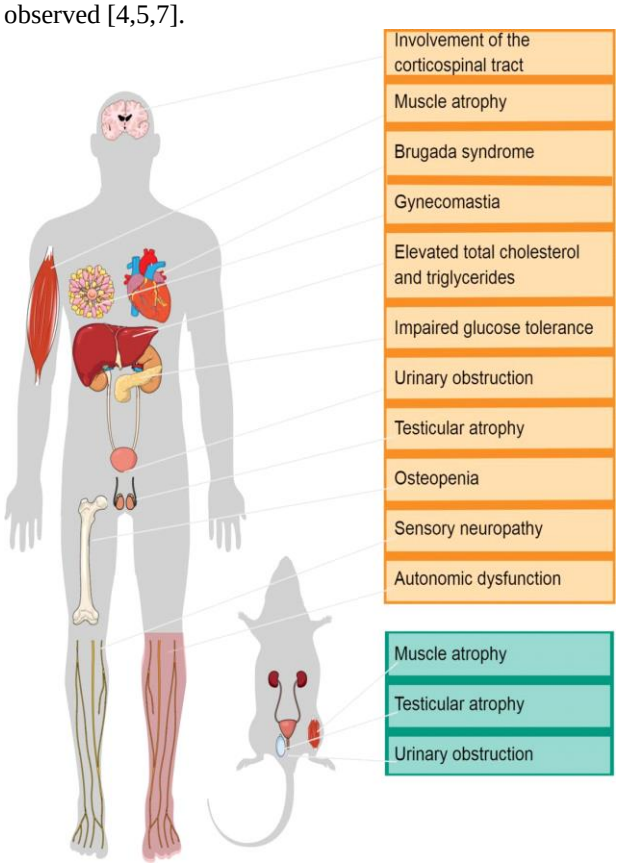


Figure 03: Clinical features of Kennedy's disease in man and mouse [7]. (Men are the ones usually affected with the condition, and women are merely carriers.)

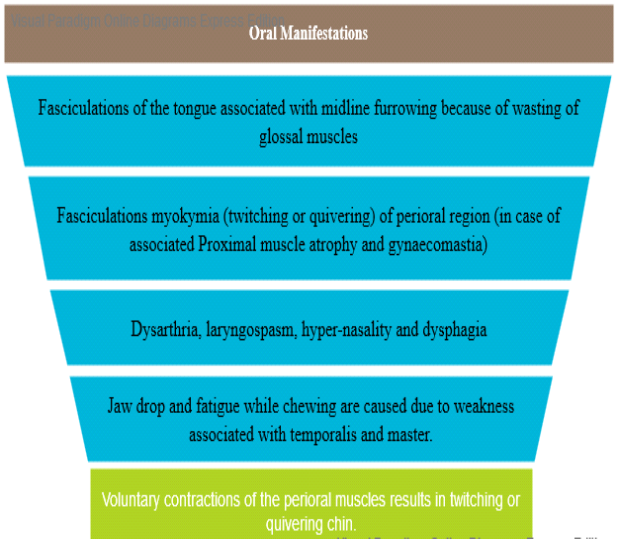


Figure 04: The oral manifestation of SBMA [4,5,7]

Sensory manifestation:

Sensory symptoms like numbing and tingling, mainly in the distal portion of limbs, is observed in later courses of the disease. In a study by Antonini et.al, in 2000, on the sensory involvement in Spinal and Bulbar muscular Atrophy, the assessment indicated the presence of trigeminal neuronopathy [8].

Others:

Signs of androgen insensitivity, such as testicular atrophy, gynecomastia, oligospermia, and erectile dysfunction and decreased sperm count are observed in SBMA affected males. Carrier females have reported cramping and other symptoms [7]. Obstructive sleep apnea is common in SBMA patients. Brugada-like ECG abnormalities are observed in 4% patients and should be monitored closely [5].

Investigations:

- Appropriate family history is the first and foremost in diagnosis of the disease.
- Low sensory neuron actionable potential (SNAP) amplitude and histopathological studies implies sensory neuronopathy [7].
- Genetic testing for CAG repeats in Androgen Receptor is deemed necessary. The normal level of CAG repeats varies from 11-32 CAGs and the SBMA population portrays 38-69 [5].
- Laboratory findings like elevated serum creatine kinase (2-4 times increase) [9], aspartate and alanine aminotransferase and lactose dehydrogenase(useful biomarkers evidently showing skeletal muscle involvement), liver enzymes, total cholesterol , LDL, triglycerides [7].
- Serum creatinine is considered a useful biomarker in diagnosing the disease in a study conducted by Hijikata et.al, 2018 [10].
- Electrophysiologic studies
- PET scans revealed Glucose hypo-metabolism in frontal lobe areas.
- Histopathological studies
- Swallowing deficits are identified by Video fluorography with Barium swallow [5,9].

Differential diagnosis:

Differential diagnosis includes ALS, hereditary causes like SMA type IV, dHMNs (distal hereditary motor neuropathies). Symptomatic similarities exist between metabolic myopathies, myasthenia gravis and polymyositis. Other non-hereditary mimics includes Progressive Muscular Atrophy (PMA), post-polio syndromes, Paraneoplastic syndrome (PNS), toxins like lead poisoning, etc [5].

Prognosis:

It has been observed that these patients show good mobility preservation until the late stages of disease. Patients can initially reveal dysarthria, which may progress to dysphagia. Although the life expectancy is not significantly reduced, risk of choking and aspiration pneumonia are higher in selected patients due to bulbar dysfunctions[5].

Management and current trends:

The target of clinical trials conducted is to reduce the Androgen Receptor ligand repeats in SBMA patients, but this has not been the case of the therapeutic strategies experimented till date.

Table 01: The given table summarises completed studies according to Author, Year and the study performed and their outcomes [5].

Author, Year	Study done	Outcome
Katsuno et.al, 2003	Leuprorelin rescues polyglutamine-dependent phenotypes in a transgenic mouse model of spinal and bulbar muscular atrophy.	In transgenic mouse models- Positive outcome
Fernandes et.al, 2011	Efficacy and safety of Dutasteride in patients with spinal and bulbar muscular atrophy: a randomised placebo-controlled trial.	No effect
Querin et.al, 2013	Pilot trial of Clenbuterol in spinal and bulbar muscular atrophy	Increase in the 6-min walk test and forced vital capacity after 12 months.
Hashizume et.al, 2017	Long-term treatment with Leuprorelin for spinal and bulbar muscular atrophy: Natural history-controlled study.	Recent study conducted in man-delay the functional decline and suppress the incidence of pneumonia and death in SBMA patients

2. Spinal Muscular Atrophy:

The term "spinal muscular atrophy (SMA)" refers to a group of genetic disorders characterized by degeneration of anterior horn cells and resultant muscle atrophy and weakness. Currently, data reveals the incidence rate of this disease to be 1:11,000. Male population is more affected [11].

Genetic involvement:

It was first revealed in 1995, in Melki Laboratory that 95% of SMA cases reported, are caused by homozygous deletion of SMN (Survival Motor Neuron) 1 gene on chromosome 5q13 [12]. In humans, two forms of SMN gene exists: a telemeric form (SMN 1) and centromeric form (SMN 2). Patients lacking a functioning SMN 1 gene, are dependent on SMN 2 gene, to produce the SMN protein. Due to exclusion of exon 7 in 85% of the cases, the SMN protein renders non-functional. This leads to deficiency of the SMN protein and in turn causes SMA [13].

Pathophysiology:

SMN functions as a multiprotein complex and is found throughout the cytoplasm and nuclei, which is important in splicing and ribonuclear biogenesis. Another school of thought is the downstream consequences of altered RNA processing that results in non-favourable motor neuron survival or development or both [13].

Clinical features:

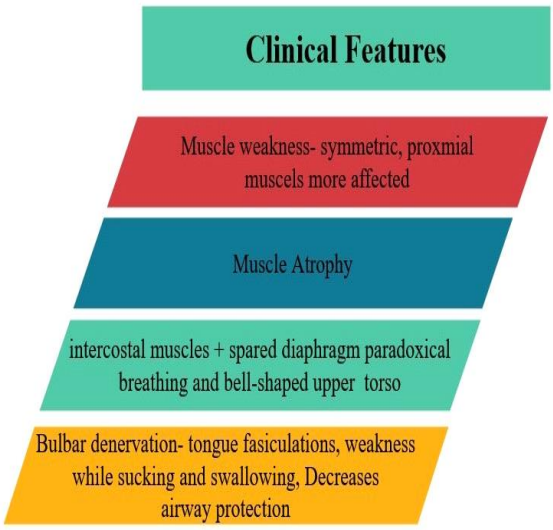


Figure 05:The given chart summarises the general clinical features observed in SMA patients [13,14]

SMA doesn't have any major oral manifestations. It was presented with multiple phenotypes which were categorised into 4 types in 1991 by the Muscular Dystrophy Association. The classification was based on motor function and age of onset. (Table 02).

TABLE 02: The table summarises the classification of SMA on the basis of motor function and age of onset [1].

TYPE	ONSET	INHERITANCE	FEATURE	PROGNOSIS
TYPE 1 Werdnig- Hoffman	Infancy	Autosomal recessive	Severe muscle wasting/ weakness, Chances of respiratory failure	Poor
TYPE 2 Kugelberg-Welander	Childhood, adolescence	Autosomal recessive	Proximal weakness and wasting, EMG shows denervation	Slowly progressive disability
TYPE 3 Distal forms	Early adult life	Autosomal dominant	Distal weakness and wasting of hands and feet	Good, Seldom exhibits disability
TYPE 4 Bulbospinal	Adult life, males only	X-linked	Facial and bulbar weakness, proximal limb weakness, gynaecomastia	Good

Investigation:

Table 03 : The table summarises the different diagnostic criteria for determining the presence of Spinal Muscular Atrophy [12]

• Familial history
• Presence of proximal muscle weakness,
• Reduced/ absent deep tendon reflexes
• Identify variants of SMN1 on molecular genetic testing

Differential Diagnosis[15]:

Congenital- Myotonic Dystrophy Type 1, Congenital Muscular Dystrophy, Congenital Myasthenic Syndrome,etc

Later Childhood- Guillain Barre Syndrome, Hexosaminidase A deficiency, Monomelic Amyotrophy,etc

Adulthood- Spinal and Bulbar Muscular Atrophy, Amyotrophic Lateral Sclerosis

Prognosis-

The new developments in management of this neuronal condition, will presumably improve the natural history of the condition. Newborn screening programs, targeted therapy and diagnosis prior to development of symptoms, will decrease the morbidity and mortality [15].

Management:
The past decade has shown marked improvement in the clinician's ability to manage patients of this neuronal condition.

Table 04: The table summarises the different organ systems that need evaluations and the possible assessments, evaluation and aids that can be done [15].

Organ System	Aids
Gastrointestinal/ Feeding	• Evaluate for Feeding dysfunction, Gastroesophageal reflux,Constipation; • Consider gastric tube placement in cases with dysphagia or aspiration risk
Respiratory	• Evaluate for Forced Vital Capacity (FVC), Assess pulse oximetry and capnography, airway clearance, Consider Polysomnogram • Refer to a pulmonologist • SMA I and II are generally weak, and are of concern for nocturnal hypoventilation
Musculoskeletal	• Orthopaedic therapy, physiotherapy, Occupational Therapy evaluation and rehabilitation is important • Assess the gross and fine motor skills • Contractures and hip dislocation Scoliosis • Need for ambulatory aids
Miscellaneous	• Genetic counselling • Family support and resources • Use of community or online resources Need for social work involvement Home nursing needs

CURRENT ADVANCEMENTS IN SMA TREATMENT:

- Lunn, in 2008, tabulated various clinical trials that were ongoing or completed in molecular genetics. He concluded that the implications of these trials will improve the standard of care for patients and cure this devastating neurodegenerative disease [14].
- Many different methods like small molecule therapy, RNA- based therapy and gene therapy have evolved.
- In 2016, The Food and Drug Administration approved the use of NUSINERSEN (SPINRAZA) . The recommended dosage is administered intrathecally in doses of 12 mg (5 mL). The treatment is initiated by 4 loading doses of the drug. The first 3 doses are given in a 14 days interval and the last one is administered 30 days after the 3rd dose. Every 4 months after the 4th dose, a maintenance dose is provided [16].
- In a study by Mendell and his colleagues reported in 2017, 15 patients with SMA 1 were provided with a single dose of IV adeno-associated virus serotype 9 carrying SMN complementary DNA encoding the SMN protein. 3 patients received low dose, and 12 received high dose. All patients were alive and event free for a period of 20 months. Of those patients who received high doses, 11 were able to sit unassisted, 9 were able to roll over and could speak and 2 of them were able to walk independently. The use of prednisolone was observed to increase the serum aminotransferase levels in 4 patients. It resulted in a longer survival rate, making the patient achieve motor milestones and accentuate their inherent motor functions. But, due to smaller study group, further studies are required to confirm the findings of this single gene therapy [17].

3. Distal Hereditary Motor Neuropathy (dHMN)

Distal Hereditary Motor Neuropathies (dHMN) are a group of genetically occuring heterogeneous diseases due to LMN weakness. The condition is thought to begin during the first two decades but onset in the third decade is also common [18].

Classification:

Table 05: The given table describes the different types of Distal Hereditary Motor Neuropathy, traits, features and Gene mutation as elucidated by Harding et.al, in 1993 [19].

TYPES	TRAIT	FEATURES	GENE MUTATION
Type 1	Autosomal Dominant	Juvenile onset, distal wasting and weakness	HSPB1 HSPB8
Type 2	Autosomal Dominant	Adult onset with distal wasting and weakness	HSPB1 HSPB8 BSCL2
Type 3	Autosomal Recessive	Slow progressive wasting and weakness	unknown
Type 4	Autosomal Recessive	Slow progressive wasting and weakness with diaphragmatic paralysis	unknown
Type 5	Autosomal Dominant	Upper limb predominance	GARS BSCL2
Type 6	Autosomal Recessive	Spinal muscular atrophy with respiratory distress type 1	IGHMBP2
Type 7	Autosomal dominant	Adult onset with vocal cord paralysis	DCTN1 TRPV4
X-linked dHMN	X-linked	Distal-onset wasting and weakness	ATP7A
dHMN and pyramidal features	Autosomal dominant	DHMN with pyramidal features	SETX BSCL2

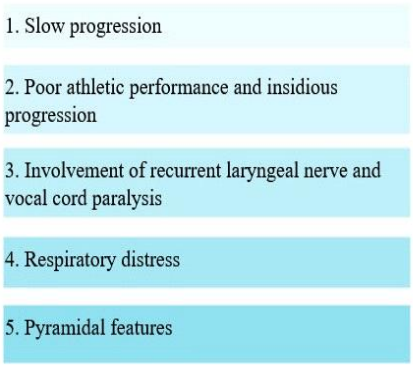


Figure 06: The given figure elucidates the cardinal features of Distal Hereditary Motor Neuropathy [18]

Upper limb predominance, Vocal Cord paralysis, respiratory distress and pyramidal features are seen in some patients [4]. Oral manifestations are not majorly manifested.

Investigation:

- In EMG chronic distal predominant denervation is observed [18].
- Neurophysiologic studies enables to differentiate between Charcot Marie and dHMN [18].
- In a genetic study by Tsai et.al, in 2017, on Taiwanese population, it was demonstrated that dHMN can be caused by mutation of WARS gene (responsible for tryptophan production and angiostasis), and identifies the probable pathogenic role of t-RNA synthetases in inherited neuropathies [20].
- Next-generation sequencing [4]

Differential diagnosis-

Myoshi Myopathy, Charcot Marie Tooth disease,etc [18].

B**. Acquired Lower motor Neuron diseases:**

1. Progressive muscular Atrophy (PMA)

Progressive Muscular Atrophy (PMA) is a rare, sporadic, adult-onset, clinically isolated LMN syndrome due to the degeneration of LMNs, including anterior horn cells and brainstem motor nuclei [21]. In 1850, a French neurologist, Aran, and Duchenne coined the term PMA. Therefore, PMA is sometimes referred to as Aran-Duchenne or Duchenne-Aran disease [22]. Cruveilhier in 1853, autopsied Aran‘s patients and revealed atrophy of the ventral spinal roots and the motor nerves providing the first evidence of PMA being a neurogenic disorder. It accounts for 5% of adult-onset MNDs. Men are more commonly affected and are found in the older age group (mean age: 63.4+/- 11.7 years) [23].

Evidence reveals subclinical UMN involvement in radiographic or neurophysiologic examination despite its clinical absence [21,24]. The life expectancy when compared with ALS patients is longer. At present, sporadic patients with MND having purely LMN symptoms on examination are termed PMA, who could possibly develop UMN features in future [21].

Pathophysiology:

It is caused by LMN and spinal cord degeneration. In a study by Geser, 2011, 43 kDa transactive responsive sequences DNA binding protein (TDP- 43) is the most commonly found inclusion body in motor neuron disease [25]. Although many genetic mutations were identified in anterior horn cell degeneration eg: SOD1, SMN1, etc; majority were absent in PMA [26]. At present, the exact pathogenesis is unknown [21].

Clinical features:

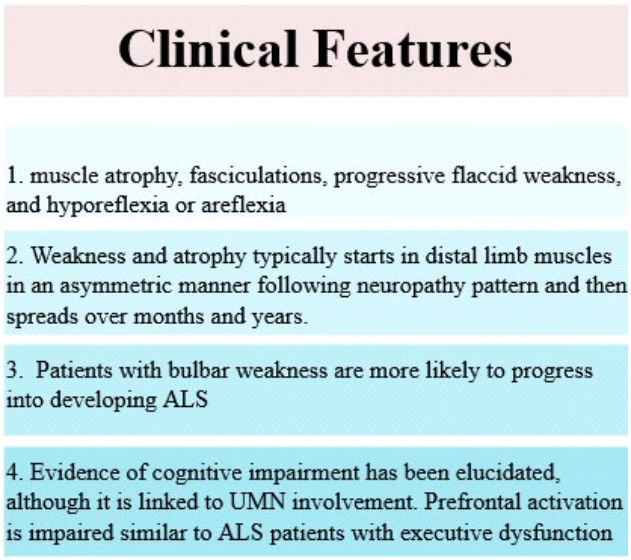


Figure 07: The given figure summarises the clinical features of PMA [21].

INVESTIGATION:

Table 06: Table given table describes the various investigations done for treating the condition briefly [26].

Electrophysiologic- It confirms active and chronic denervation
Nerve conduction studies- low to normal compound motor amplitude potential
Needle EMG- Various spinal segments reveals active denervation in forms of fasciculations, fibrillations, and unstable MUPs
Diffusion Tensor imaging- reduced fractional anisotropy along corticospinal tracts; transcranial magnetic stimulation which shows prolonged central motor conduction

Imaging biomarkers [21]:

- Imaging biomarkers of UMN involvement include diffuse tensor MRI (magnetic resonance imaging) and MRS (magnetic resonance spectroscopy).
- Neurophysiological biomarkers of UMN involvement are TMS (transcranial magnetic stimulation) and Beta-band intermuscular coherence (relatively new technique, evidentially reliable marker).

Prognosis:
Rate of progression can vary. In a comparison study by Kim et.al, in 2009, the mean survival duration in patients with PMA and ALS were estimated in 200 months. It was found that PMA patients had a 12 month longer survival period when compared with ALS patients. A shorter survival rate has been associated with several factors like: (1) axial onset, (2) ALSFRS-R at diagnosis less than 38, (3) involvement of more segmental regions, (4) baseline forced vital capacity (FVC) less than 80% of the predicted value, (5) a sharp decline in FVC within the first 6 months. Patients presenting with a history of 4 years of PMA with weakness restricted to distal or proximal muscles have a favourable prognosis [27].

Differential diagnosis [26]:
Immune neuropathies- Multifocal motor neuropathy; Paraneoplastic neuropathies;
Degenerative conditions- SMA, bulbospinal atrophy, Hirayama disease,
Amyotrophy as a dominating feature in- Tay-Sachs disease, porphyria, etc.

Management:
There is no specific management for treating patients of this neuronal population. It is recommended to follow the therapeutic strategies used in case of patients with ALS [26]. Regular surveillance and symptomatic management is considered mandatory.

Table 07- Summarises the therapies required and their intervention for ALS, as mentioned by Statland, in 2015 [3]

Therapy	Intervention
Respiratory	Non-invasive positive pressure ventilation, cough assist, oral suctioning
Speech Therapy	Percutaneous gastrostomy tube for nutrition
Hypersalivation	Include anticholinergic medication, botulinum toxin, xerostomic agents
Physical and Occupational therapy	Ambulatory services, braces, etc.
Psychological	Counselling for patients and family

2. Monomelic Amyotrophy (Hirayama Disease)
In the 1950s, Hirayama first described monomelic amyotrophy. It was later referred to as Hirayama disease (HD). It has been mainly reported to occur in Japan, China and India. It affects males mostly (Male : Female= 7:1) and in the younger age group (adolescents to 3rd decade of life) [28,29].

Clinical features:

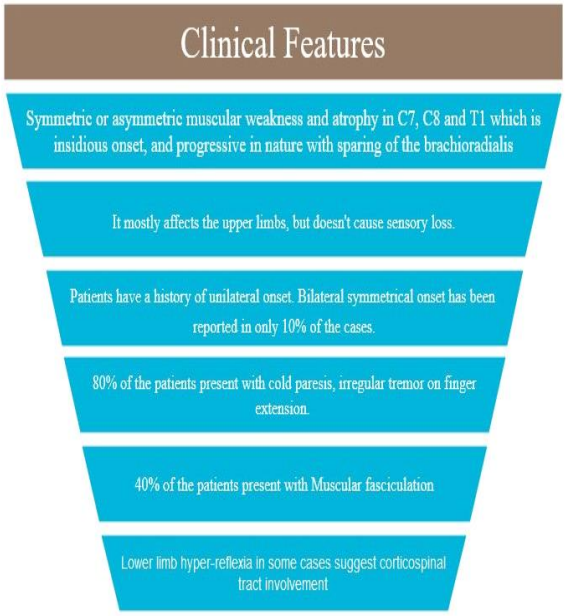


Figure 08: The given figure depicts the clinical features of Monomelic Amyotrophy [29]

Pathogenesis:
Although the pathophysiology is uncertain, it may involve damage of anterior horn cells. Displacement of the posterior cervical dural sac on neck flexion resulted in cord compression and/or venous congestion. It's non-progressive, purely motor focal amyotrophy in distribution of C7, C8, T1 spinal innervated muscles [29].

Genetic studies:
In a clinical study by Misra et.al, in 2005, on the SMN motor gene deletion in relation to Hirayama disease, it was concluded that SMN gene deletion was not found.[30]
In a mutational analysis of Glycyl- tRNA synthetase (GARS) gene in Hirayama disease, by Blumen et.al, in 2010, no pathogenic mutations were found, excluding its possibility as an etiologic factor in Hirayama Disease (HD).[31]

Investigation:
- CSF analysis, muscle enzyme levels.
- Motor nerve conduction studies reveal reduction in the ulnar compound muscle action potential (CMAP) when compared with median CMAP.
- Sensory nerve conduction studies.
- In 2006, studies on somatosensory potential by Misra et.al, revealed amplitude reduction in cervical response during neck flexion, which indicates overstretching of cervical cords due to subclinical damage to sensory fibers [32].
- MRI scans portrayed flattening of spinal cord against C5 and C6 vertebral bodies

- Electromagnetic induction helps examine motor functions [29].

Management:

- If the condition is recognized early, the use of cervical collars for a timer period of 3-4 years is considered to relieve the patient of progressive muscle weakness and thus reducing the impact of the condition [33].
- In a systematic review by Bembenek, in 2020, the use of Noninvasive brain stimulation with Transcranial Magnetic Stimulation (TMS) has been reviewed. All studies in HD patients focused on single-pulse motor evoked potentials (MEPs). The systematic review remains inconclusive due to lack of evidence. Hence, further studies are indispensable to confirm the usefulness of this method [34].

C. Acute Lower Motor Neuron Diseases:

1. Post- polio Syndrome (PPS)

PPS is an acute type of LMN that occurs many years following episodes of poliomyelitis [35]. It usually occurs after 30 to 40 years after initial polio virus attack. It is more commonly seen in females. It is characterised by progressive weakness and atrophy of joints and muscle pain[36]. 15-80% of paralytic polio survivors develop post-polio syndrome. A recent study, by Bertolasi et.al, in 2016, on a 50 year follow up of Polio patients in North Italy, revealed the prevalence of the disease to be 42% [37].

Pathophysiology:

There is a marked increase in motor unit areas caused by collateral sprouting of adjacent motor neurons in the spinal cord. The motor unit area is said to increase upto 20 times, reaching a level where no further reinnervation is possible. Due to uncompensated denervation, loss of muscle strength and atrophy of muscle fibers occurs. The underlying cause of denervation is still unclear. The different hypotheses that have been proposed are [38]:

- stress or overuse of motor units
- Ageing
- Persistent virus
- Immunological factors and chronic inflammation
- Genetics

Gene involvement:

- Bartholdi et. al, in 2000, in his brief report on the gene involvement in PPS, identified the absence of SMN gene deletion [39].
- In 2002, Rekand et. al, and his colleagues, identified polymorphism in Fc- gamma receptor III A as a causative factor of post-polio syndrome [40].
- In 2014, in a study by Saurabh Kumar et.al and his colleagues, out of 110 patients, only 50 patients (45.46%) showed polymorphism in exon 2 of PVR gene. They concluded that the disease progression is associated with PVR gene [41].

Diagnostic criteria:

The diagnostic criteria for Post-poliomyelitis are, period of recovery following acute poliomyelitis, gradual onset of muscle weakness, joint pain, sleeping problems and prior paralytic poliomyelitis.

Investigation:

Table 08: The given table summarises the various clinical signs and investigations [38].

	Clinical signs	**Investigation**
Muscle function	Weak or no muscle strength, flaccid paralysis	Clinical examination Electromyography MRI
Tendon reflexes	Weak or no tendon reflexes	Clinical examination
Sensory function	No sensory loss, cold intolerance might be present	Clinical examination Nerve conduction velocity
Cranial nerves	Most often normal but might be impaired (bulbar poliomyelitis)	Clinical examination Investigation on oesophageal and laryngeal muscle function
Pulmonary function and sleep-disordered breathing	Weak respiratory muscles, chest wall and spinal deformities Daytime sleepiness	Pulmonary investigation, including complete spirometry Polysomnography

Differential diagnosis:

Conditions like Amyotrophic Lateral sclerosis, tumors of the cervical and thoracic cord cervical spondylosis, other causes of chronic fatigue syndrome, myasthenia gravis, myopathies and chronic systemic infections are are the differential diagnosis for PPS [36].

Management:

There is no cure of PPS. Symptomatic treatment that improves the quality of life is the main goal in management of the condition. Symptomatic management can be dealt with analgesics and antidepressants.

Physiotherapy, physical activity and muscle training:

The European Neuromuscular Centre Workshop in 1994, recommended guidelines for exercise that are still valid.

TABLE 09: The given table describes the condition of the patient and the physical training that can be done for the patient [38].

Condition of the patient	**Physical Training**
Near- normal strength, no signs of reinnervation	Heavy resistance training
Moderate Paresis with signs of reinnervation	Submaximum Endurance Training
Severe Paresis	Avoid muscle training.

Pharmacological treatments:

TABLE 10: The given table discusses about the different clinical trials done in the field of Pharmacology in management of Post-Polio Syndrome [38].

Author, Year	Clinical Trials	Outcome
Horemans et.al, 2003	Pyridostigmine in postpolio syndrome: no decline in fatigue and limited functional improvement.	A marked improvement in walking
Gonzalez et.al, 2004	Prior poliomyelitis-IVIg treatment reduces proinflammatory cytokine production.	Marked decrease in the quantity of proinflammatory cytokines
Vasconcelos et.al, 2007	Modafinil for treatment of fatigue in post-polio syndrome: a randomized controlled trial.	Ineffective
Skough et.al, 2008	Effects of resistance training in combination with coenzyme Q10 supplementation in patients with post-polio: a pilot study.	No significant result

Surgery:

Limb length inequality, joint deformities and arthrosis require surgery. Secondary disorders like spinal stenosis, disc hernia require surgical intervention.Due to increased sensitivity of patients of this neuronal population to anesthetics, the patient should be monitored carefully throughout the procedure [38].

- **Guillain Barre Syndrome (GBS)**

It was initially described in 1916 [42]. GBS is characterised by rapidly progressive weakness of arms and legs and in some patients involves the bulbar and respiratory muscles too [43]. GBS incidences vary between 0.4 and 3.25 cases per 100,000 per year. It occurs due to precipitated infection. Infectious agents like cytomegalovirus, herpes simplex virus, Epstein Barr virus, Influenza, etc, have been found to be associated with the disease. Recent surgeries have also found to be associated with the condition [44].

Pathogenesis:

It is a post-infectious immune-mediated nerve injury of 3 phenotypes: (1) Purely demyelinating (2) Purely axonal (3) demyelinating with axonal involvement. It is an antibody mediated reaction. Antibodies binding to GM1 or GD1a gangliosides activate myelin destroying complements [42].

Clinical features:

Table 11: The given table describes the different clinical features of Guillain Barre Syndrome [42.44]

Severe back pain, distal limb parasthesia- " tight band" feeling
Areflexia and weakness
Weakness- Rapid, ascending pattern Weakness of oropharyngeal and facial muscles
Dysesthesia of feet and hands
Symmetric limb weakness, decrease or loss of reflexes and objective sensory findings
Ophthalmoparesis- a rare finding (Associated with Miller-Fisher Syndrome)

Investigation-

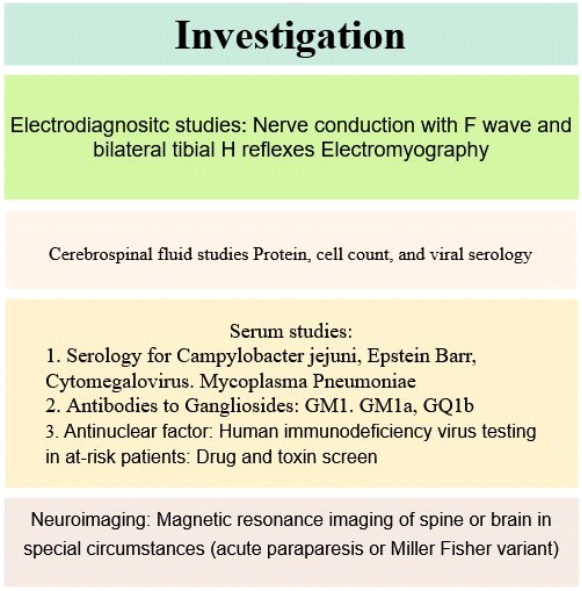


Figure 09: The figure elucidates carious Investigations required for Guillain Barre Syndrome [42]

Management:

Table 12: The given table describes management of Guillain Barre syndrome patients [42]

Due to loss of ambulation, expert nursing is mandatoryDue to loss of ambulation, expert nursing is mandatory
Tests checking swallowing dysfunction, aspiration risk are necessary
Enteral nutrition is necessary in many patients
Pneumatic compression devices- to avoid deep vein thrombosis in paralysed leg
Physical therapy in early stages
Cramping- relieved by narcotics; Other drugs like Carbamazepine or gabapentin are also given
Plasma therapy
IVIg

CONCLUSION:

Lower motor neuron diseases include a broad spectrum of conditions with numerous pathologic and genetic causes. It is important to combine clinical assessment with neurophysiologic findings so as to establish accurate diagnosis. The recent advancements in genetic studies and imaging techniques have increased the quality of life for the patient and has magnified the treatment options available. Although the studies conducted provide a positive outcome, some of them lack prospective evidence. Nevertheless, the genetic analysis and developing imaging techniques are bound to bring forth a better insight into understanding the pathophysiology of various lower motor neuron diseases prevalent. This is turn will enable the medical and paramedical practioners to gain a better insight in managing patients with these conditions.

Ethical approval: Not applicable

Acknowledgement: None.

Conflict of Interest: The authors have no conflict of interest.

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