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Advances in understanding and managing Motor Neuron Disorders: From Pathophysiology to Therapeutic Interventions

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ABSTRACT

Motor neuron disorder (MND), also known as ALS, is a spectrum disorder that leads to the deterioration of corticospinal and alpha motor neurons, resulting in weakness in muscles such as those in the abdomen and bulbar region. It also affects eye muscles and sphincter function. Research suggests that approximately 2 out of every 100,000 people worldwide are affected by MND, causing muscle weakness, paralysis, speech difficulties, swallowing problems, and severe respiratory issues. ALS has both genetic and environmental causes, as well as various presentations. Early recognition of symptoms and appropriate laboratory evaluations are crucial to prevent diagnostic delays and misdiagnosis. Recognizing related motor neuron diseases can help provide proper counselling to patients and prevent misdiagnosis. This review aims to explore advances in understanding and managing motor neuron diseases, including their pathophysiology, diagnosis, types, current therapeutic approaches, pharmacological treatments, symptomatic and supportive care, and emerging therapies for future directions and management

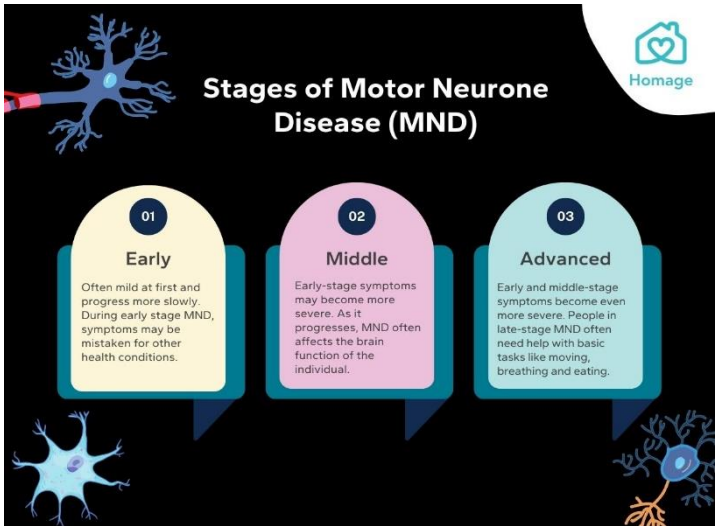
Key Words: *Dysarthria, dysphagia, corticospinal neurons, ALS, upper motor neurons , lower motor neuron*

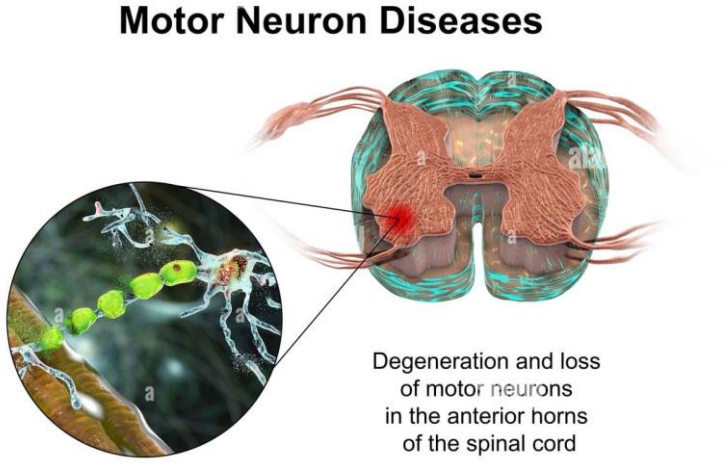
1. INTRODUCTION

Motor Neuron Disorders (MNDs) are characterized by the progressive loss of motor neuron that control voluntary muscle movements. These are; The degeneration of upper motor neurons that are located in the motor cortex in the brain. Lower motor neurons that link spinal cords to muscles.(1) This causes neuromuscular disabilities and serious illness, which eventually leads to significant disability and death, usually within three years. Given the clinical and pathological heterogeneity of MND, it has been challenging to identify therapeutic targets. However, Progress in recent years has stimulated innovative research into this devastating disorder.(4)MND poses a clinical challenge due to its progressive nature and significant impact on motor function and quality of life.(1)

Definition of MNDs -

Motor neuron diseases include a number of disorders including Amyotrophic Lateral Sclerosis (ALS) where both motor neurons (UMNs) and lower motor neurons (LMNs) are involved to a steady decline in the muscular system. Spinal muscular atrophy (SMA) mainly affects LMNs and is usually a hereditary disease. While ALS affects lower motor neurons, PLS only affects UMNs and progresses slowly, and although PBP similarly progresses, it affects the muscles essential for speaking and swallowing.(3)





CLASSIFICATION OF MNDs

Motor neuron disorders are typically categorized into four groups:

1. **AMYOTROPHIC LATERAL SCLEROSIS (ALS):** THIS IS THE MOST COMMON;, PYRAMIDAL OR UPPER MOTOR NEURON TYPE LESION INVOLVING THE LMN'S AS WELL.
2. **SPINAL MUSCULAR ATROPHY (SMA):** THIS IS AN INHERITANCE DISEASE THAT ESPECIALLY OCCURS IN CHILDREN AND PREDOMINANTLY INVOLVES LMNS.
3. **THE OTHER KIND OF DISEASE OF ALS**, CALLED PRIMARY LATERAL SCLEROSIS (PLS) MAINLY AFFECTS ONLY UPPER MOTOR NEURONS (UMNS) AND SYMPTOMS APPEAR TO BE LESS SEVERE AND PROGRESS MORE SLOWLY.
4. **PROGRESSIVE BULBAR PALSY (PBP)** PARTICULARLY IMPLICATES BULBAR MUSCLES, WHICH CAUSE SPEAKING AND SWALLOWING PROBLEMS.

An estimated incidence of ALS is sixty cases per one hundred thousand individuals worldwide, nevertheless the global incidence rates ranging from 2-3 per one hundred thousand population annually. SMA is less frequent than other genetic causes of infant mortality, affecting one of ten thousand children born alive.([2])

With increased awareness of how prevalent these diseases are researchers have shifted their attention towards discovering more on the causes and cure for these diseases.([1])

GLOBAL IMPACT AND PREVALENCE

Globally, there were 63,700 incident cases and 268,673 prevalent cases of MHD, according to GBD estimates for 2019. In 2019, MND resulted in 39,081 deaths and 1,034,606 DALYs worldwide. North America, Western Europe, and Australia are three high-income regions where more than half of the prevalence and deaths from MND occurred. In high-income East Asia, the prevalence, incidence, and DLAYs of MND were relatively low when compared to similar sociodemographic index groups elsewhere, but they were generally higher in regions with high sociodemographic indices.

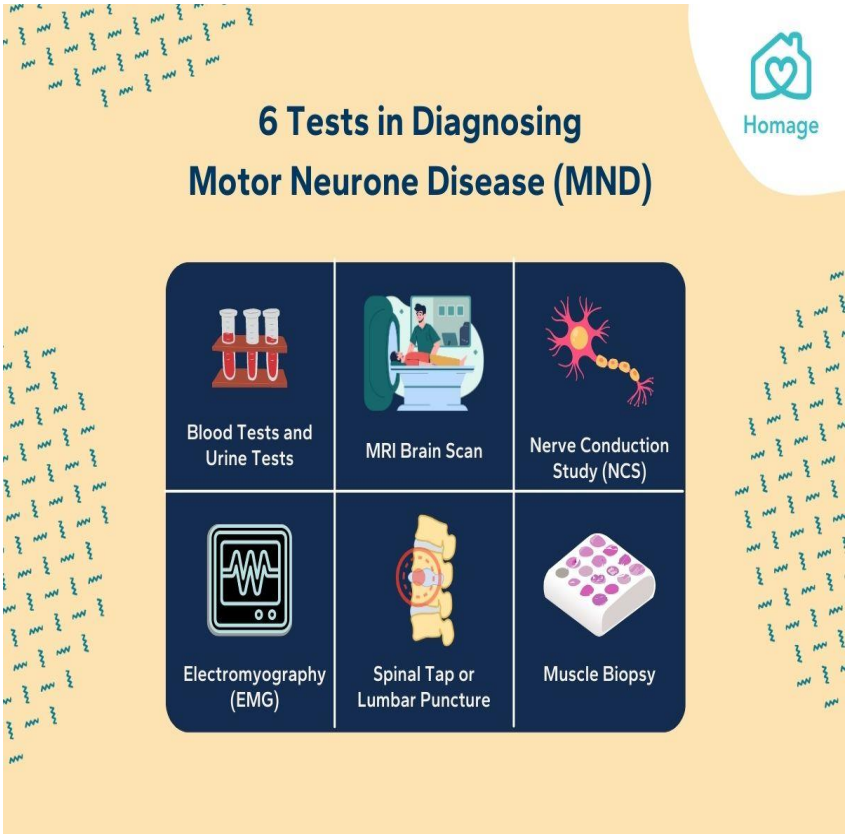
Between 1990 and 2019, the prevalence of MND increased. Its projected growth emphasizes the importance of global and national healthcare planning based on more objective evidence. Geographical variation in the burden of MND may indicate the impact of genetic background and sociodemographic status in different areas.([5])

II. PATHOPHYSIOLOGY OF MOTOR NEURON DISORDERS

MNDs are known to occur due to interplay of genetic and molecular influences and environmental factors as well and lead to motor neuron death. ALS approximately 10% is inherited; it is caused by mutations in genes such as SOD1, C9ORF72, TARDBP, and FUS.(1)

Neurodegeneration in Motor Neurons

ALS not this both UMNs and LMNs characterized by the disconnection of motor pathways needed for motor neuron function. The synergist dysfunction disrupting the motor neurons and muscles interaction, leads to muscular atrophy, weakness, and finally, the motor function is lost.(1)



Some of the factors may be genetic and environmental.

It is observed in the familial ALS that in SOD1 and C9ORF72 genes are linked to the disease. Altered SOD1 forms aggregates in motor neurons and the pathways are toxic leading to oxidative stress and cell death. On the other hand, variations in the SMN1 gene, which codes for the survival motor neuron protein, cause SMA-an illness that impacts LMNs most particularly in the **infants .(2)**

Regarding the external causes, toxins, smoking, and Militar services are considered to have causal relationship with sporadic ALS with veterans at a higher risk as well. Sources show that exposure to pesticides / Heavy metals might increase the risk of ALS according to the risks evaluated by Brown and Al-Chalabi in 2017**.(1)**

Molecular etiology (Stress Oxidative, Aggregation protein, etc.)

1. Free radical generation or oxidative stress in ALS is the state where the generation of ROS surpasses the antioxidant defences of the cells leading to cell damage. Changes in the SOD1 gene are involved in oxidative stress which distorts the proper functioning of the cells. Protein aggregation plays a significant role in the development of ALS. The accumulation of TDP-43 within neurons leads to abnormal cell function, while aggregation of FUS gene mutations is associated with RNA dysfunction. Mitochondrial dysfunction leads to reduced energy production, leading to apoptosis and exacerbating the degeneration of neurons.(1)

III.CLINICAL PRESENTATION AND DIAGNOSIS

Early Symptoms and Disease Progression.

Early symptoms of ALS are muscle weakness in the arms or legs, and slurring of speech and difficulty in swallowing. In the advanced stages, they manifest and are severe, characterized by profound muscle atrophy with reduced power of

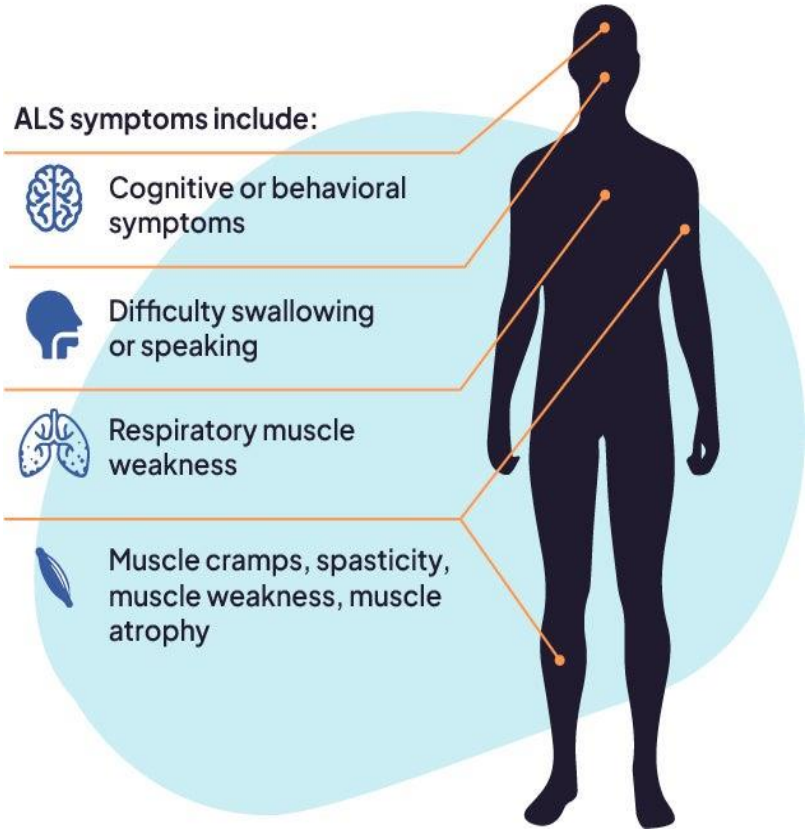
controlling movements. The symptoms of SMA begin variably, starting from infancy with severe symptoms or develop symptoms in later years of life without severe symptoms.(²)

Diagnostic Techniques (Imaging, Electromyography, Genetic Testing) .
MNDs can be diagnosed clinically by presence of classical features like denervation that can be detected by an Electromyography (EMG). Use of MRI to rule out other possible causes of neurological dysfunction like tumours is one that is used to reduce the number of patients with this condition. Medical genetics is particularly significant in predicting SMA and familial ALS because it defines gene alterations such as SMN1 and SOD1 that confirm the diagnosis and contribute to treatment programs.

Differential Diagnosis of MNDs
MNDs should be differentiated from other neurological disorders like multifocal motor neuropathy or myasthenia gravis. For instance, multifocal motor neuropathy has disparities of weakness in extent and has immunotherapy as one method of treatment, a factor that makes it differs from ALS.

IV. TYPES OF MOTOR NEURON DISORDER

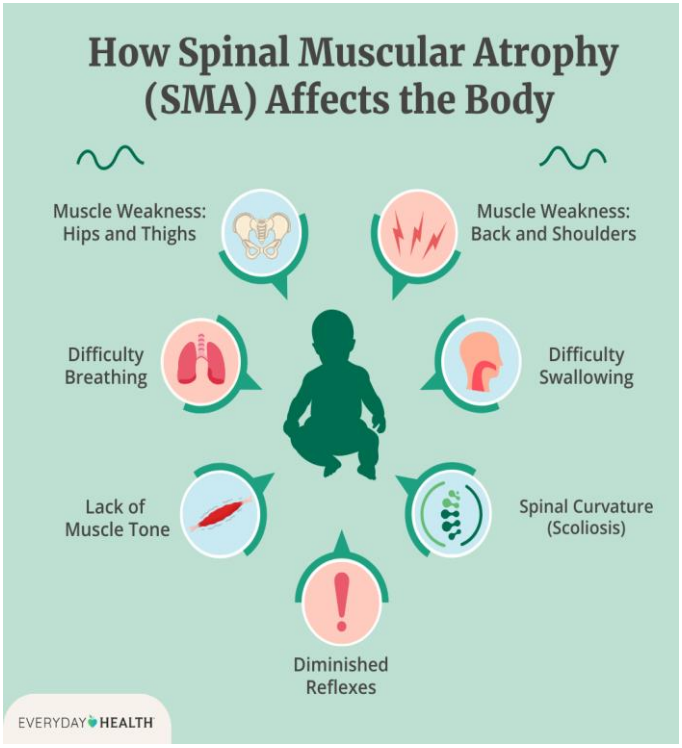
Amyotrophic Lateral Sclerosis (ALS)
ALS interferes with both upper motor neurons and lower motor neurons causing the muscle progressively to lose strength and tone. Common symptoms include difficulty in coordinating movements in the muscles which coordinate activities like swallowing and talking, progressing to the need for help with breathing.(¹)



ALS patients typically do not exhibit a level of severe autonomic impairment that could affect their quality of life. Upper motor neuron involvement has been linked to more severe autonomic deficits. (6)

Spinal Muscular Atrophy (SMA)
SMA is a genetic disorder that arises from mutations to SMN1 gene and is characterised by the loss of lower motor neurons and muscle atrophy. The muscle weakness in SMA may also differ in the degree: SMA Type 1 is considered the most severe form, which occurs in infancy, whereas

SMA Type 3 is the mildest. (²) SMA Type 3 is the mildest. (²)
SMA is diagnosed when a person has a history of motor difficulties or regression, proximal muscle weakness, reduced/absent deep tendon reflexes, evidence of motor unit disease, and/or biallelic pathogenic variants in SNM1 identified by molecular genetic testing. Increasing the copy number of Smn2 can affect the phenotype.(7)



Primary Lateral Sclerosis (PLS)

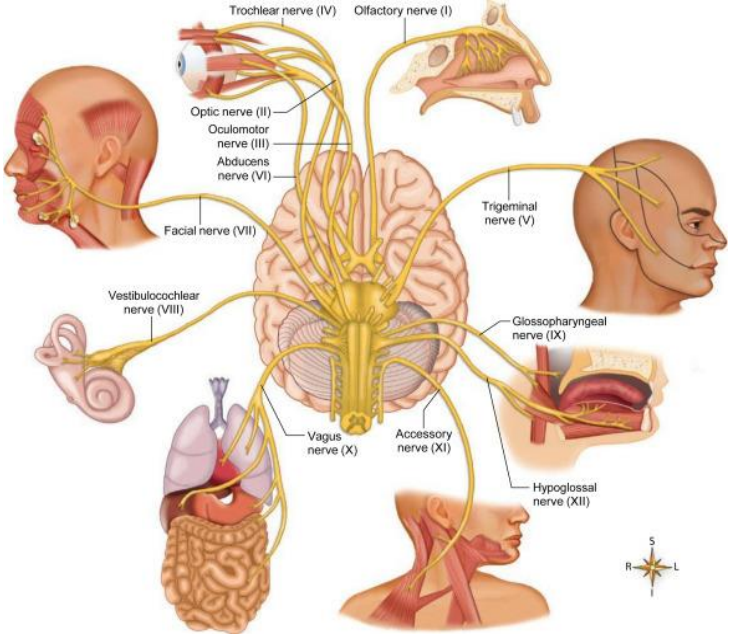
PLS affects only UMNs and is a slowly progressive disease with less severe presentation in comparison with ALS. Symptoms of PLS include muscle stiffness, raised tone in muscles, and do not include the lower motor neuron involvement like ALS.(²)

Although it may share some clinical features overlapping with ALS, especially in the early phase, PLS is marked by the absence of clinical involvement of the lower motor neurons (LMNs) and by a more protracted clinical course with a better prognosis. (8)

Progressive Bulbar Palsy (PBP)

It is considered as the same as ALS and can lead to complications with breathing as it progresses and it deter ones quality of life**.(1)**

Progressive bulbar palsy is a motor neuron disease that affects the brainstem, including swallowing, speaking, and chewing. The nerves affected are the glossopharyngeal, vagus, accessory, and hypoglossal nerves.(9)



V. CURRENT THERAPEUTIC APPROACHES

Pharmacological Treatments (Riluzole, Edaravone)

1. Riluzole acts as a glutamate antagonist, which reduces the excitotoxicity, and when given to an ALS patient, slows down the disease's progression, by about three to six months on average.

2. The FDA approvededaravone as a treatment for ALS, not only does it work as an antioxidant, which helps counteract oxidative stress, many nations across the world have approved it for use in ALS. It gives a small improvement in functional decline.([1])

Symptomatic and Supportive Care

Hearing and speech, motor and sensory, feeding and swallowing, and other physical symptoms require prescribed treatment involving exercises, speech therapies, nutritional support, etc. However it is important to ensure that respiratory support is offered using non-invasive ventilation as the respiratory muscles fail.([1])

Role of Physiotherapy and Assistive Devices

Physiotherapy is important for maintaining the patient's movement and joint flexibility and using aids like wheel chairs and communication devices for day to day activities. These frameworks are a significant help in improving patient mobility and, in Extension, the quality of their lives.([1])

VI. EMERGING THERAPIES AND FUTURE DIRECTIONS

Gene Therapy and RNA-based Therapies

Core business operates in gene therapy, in particular, Spinal Muscular Atrophy (SMA) such as Zolgensma, and the aim is to replace the deficient SMN1 genes. Some treatments target mRNA molecules to increase SMN protein and thereby improve SMA individuals survival and motor function as does Spinraza .([2])

Stem Cell Therapy

Stem cell approaches are oriented towards the replacement of the damaged neurons, or the creation of conditions that will be conductive for their functioning. In Research proposal:
The first findings reveal that there could be chances of halting the progression of ALS, even though there is a problem of achieving a long-term result despite of these advances.([2])

Neuroprotective Strategies and Drug Development

New drugs are being made with the targeted objective of maintaining neurons alive through the preservation of mitochondria and avoiding formation of proteins. Approaches to neuroprotection are based on the understanding of the molecular mechanisms of ALS and other motor neuron disorders.([2])

VII. CHALLENGES AND OPPORTUNITIES IN MND RESEARCH

Barriers to Effective Treatment

Developing effective therapies for MND is a Special case because of the heterogeneity of the disease and the blood-brain barrier that hampers the delivery of molecules into the brain. Personalized treatment plans together with focused gene therapy are more encouraging but require further enhancement according to Hardiman et al. (2017).

Advances in Biomarker Discovery

Currently, diagnostic tests like the neurofilament proteins will be valuable to detect the diseases early and to check your progress. This is becoming essential for prognosis and, more importantly, for designing effective therapies that are currently lacking.([1])

Patient-Cantered Approaches in Clinical Trials

The blending of patient-oriented outcomes to research emphasizes features of a patient's condition that are most essential, thus ensuring that treatments effectively address patients' wants.([1])

VIII. CONCLUSION

MNDs are severe diseases that can hardly be treated; therefore, the development of effective drugs for MND therapy is challenging. Current treatment approaches, based on drugs and disease management, are palliative; gene and stem cell therapies – new approaches – are likely to tackle the root of the problem. Efforts hence continue in order to aid diagnosis, alter treatment and, therefore, enhance patient care and outcomes hence the importance of multiple disciplinary approaches.

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