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MOTOR NEURON DISEASE: A REVIEW

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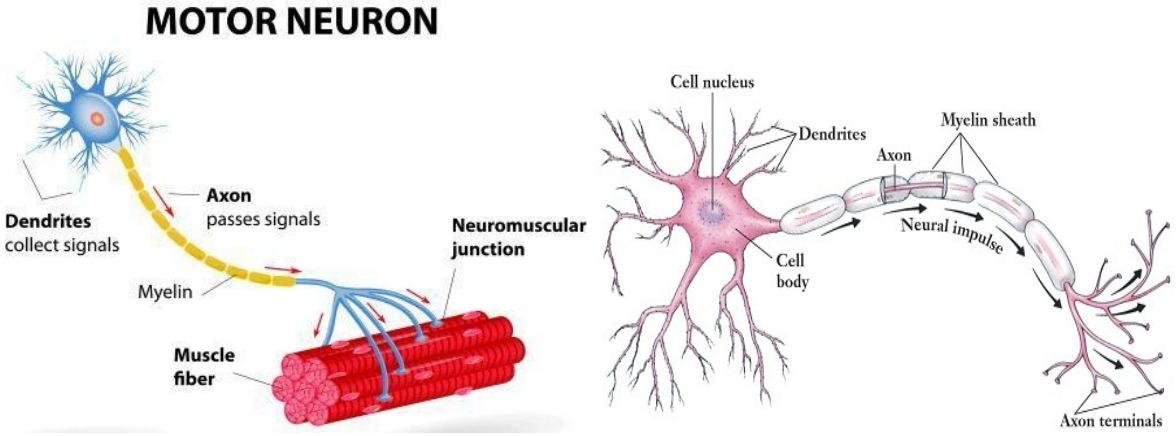
Abstract: *Motor neuron disease (MND) is characterized by muscle weakness and paralysis downstream of motor neuron degeneration. Genetic factors play a major role in disease pathogenesis and progression. This is best underscored by spinal muscular atrophy, the most common MND affecting children. Although SMA is caused by homozygous mutations in the survival motor neuron 1 (SMN1) gene, partial compensation by the paralogous SMN2 gene and/or genetic modifiers influence age of onset and disease severity. SMA is also the first MND that is treatable thanks to the recent development of a molecular-based therapy. Evidence suggests that dysregulation of autophagy plays a role in neurodegenerative diseases, including motor neuron disorders. Herein, we review emerging evidence indicating the roles of autophagy in physiological motor neuron processes and its function in specific compartments.*
Keywords: *Amyotrophic lateral sclerosis, Animal model, Motor neuron disease, SMA, SMN and Spinal muscular atrophy.*

Introduction: The motor neuron diseases (MNDs) are a group of progressive neurological disorders that destroy motor neurons, the cells that control essential voluntary muscle activity such as speaking, walking, breathing, and swallowing. Normally, messages from nerve cells in the brain (called *upper motor neurons*) are transmitted to nerve cells in the brain stem and spinal cord (called *lower motor neurons*) and from them to particular muscles. Upper motor neurons direct the lower motor neurons to produce movements such as walking or chewing. Lower motor neurons control movement in the arms, legs, chest, face, throat, and tongue. Spinal motor neurons are also called anterior horn cells. Upper motor neurons are also called corticospinal neurons.



When there are disruptions in the signals between the lowest motor neurons and the muscle, the muscles do not work properly; the muscles gradually weaken and may begin wasting away and develop uncontrollable twitching (called *fasciculations*). When there are disruptions in the signals between the upper motor neurons and the lower motor neurons, the limb muscles develop stiffness (called *spasticity*), movements become slow and

effortful, and tendon reflexes such as knee and ankle jerks become overactive. Over time, the ability to control voluntary movement can be lost [1].

Progress is relentless and generally rapid, with a life expectancy of between two and five years from the onset of symptoms. Approximately 20% of patients can survive for 5-10 years but the rate of progression varies greatly from one person to another. Death usually occurs due to respiratory failure. The incidence of MND is 2 per 100,000 of total population, while prevalence is six per 100,000 of total population. Research has found that the incidence is higher in people aged over 50 years. Only 10% of cases are familial (inherited) with the remaining 90% sporadic. The male to female ratio is 2:1 [2].

Risk: MNDs occur in adults and children. In children, particularly in inherited or familial forms of the disease, symptoms can be present at birth or appear before the child learns to walk. In adults, MNDs occur more commonly in men than in women, with symptoms appearing after age 40.

Causes Motor Neuron Diseases: Some MNDs are inherited, but the causes of most MNDs are not known. In sporadic or noninherited MNDs, environmental, toxic, viral, or genetic factors may be implicated.

Classified: MNDs are classified according to whether they are inherited or sporadic, and to whether degeneration affects upper motor neurons, lower motor neurons, or both. In adults, the most common MND is *amyotrophic lateral sclerosis (ALS)*, which affects both upper and lower motor neurons. It has inherited and sporadic forms and can affect the arms, legs, or facial muscles. *Primary lateral sclerosis* is a disease of the upper motor neurons, while *progressive muscular atrophy* affects only lower motor neurons in the spinal cord. In *progressive bulbar palsy*, the lowest motor neurons of the brain stem are most affected, causing slurred speech and difficulty chewing and swallowing. There are almost always mildly abnormal signs in the arms and legs.

If the MND is inherited, it is also classified according to the mode of inheritance. *Autosomal dominant* means that a person needs to inherit only one copy of the defective gene from one affected parent to be at risk of the disease. There is a 50 percent chance that each child of an affected person will be affected. *Autosomal recessive* means the individual must inherit a copy of the defective gene from both parents. These parents are likely to be asymptomatic (without symptoms of the disease). Autosomal recessive diseases often affect more than one person in the same generation (siblings or cousins). In *X-linked inheritance*, the mother carries the defective gene on one of her X chromosomes and passes the disorder along to her sons. Males inherit an X chromosome from their mother and a Y chromosome from their father, while females inherit an X chromosome from each parent. Daughters have a 50 percent chance of inheriting their mother's faulty X chromosome and a safe X chromosome from their father, which would make them asymptomatic carriers of the mutation

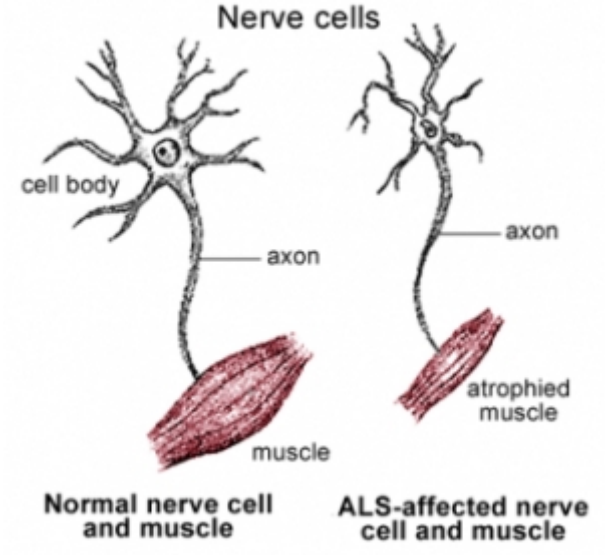
Symptoms of motor neuron diseases: A brief description of the symptoms of some of the more common MNDs follows.

Amyotrophic lateral sclerosis (ALS), also called Lou Gehrig's disease or classical motor neuron disease, is a progressive, ultimately fatal disorder that disrupts signals to all voluntary muscles. Many doctors use the terms *motor neuron disease* and ALS interchangeably. Both upper and lower motor neurons are affected. Symptoms are usually noticed first in the arms and hands, legs, or swallowing muscles. Approximately 75 percent of people with classic ALS will develop weakness and wasting of the bulbar muscles (muscles that control speech, swallowing, and chewing). Muscle weakness and atrophy occur on both sides of the body. Affected individuals lose strength and the ability to move their arms and legs, and to hold the body upright. Other symptoms include spasticity, spasms, muscle cramps, and fasciculations. Speech can become slurred or nasal. When muscles of the diaphragm and chest wall fail to function properly, individuals lose the ability to breathe without mechanical support.

Although the disease does not usually impair a person's mind or personality, several recent studies suggest that some people with ALS may develop cognitive problems involving word fluency, decision-making, and memory. Most individuals with ALS die from respiratory failure, usually within 3 to 5 years from the onset of symptoms. However, about 10 percent of affected individuals survive for 10 or more years.

ALS most commonly strikes people between 40 and 60 years of age, but younger and older individuals also can develop the disease. Men are affected more often than women. Most

cases of ALS occur sporadically, and family members of those individuals are not considered to be at increased risk for developing the disease [3,4]. Familial forms of ALS account for 10 percent or less of cases of ALS, with more than 10 genes identified to date. However, most of the gene mutations discovered account for a very small number of cases. The most common familial forms of ALS in adults are caused by mutations of the superoxide dismutase gene, or SOD1, located on chromosome 21. There are also rare juvenile-onset forms of familial ALS.



Pathogenesis: The aetiology of the vast majority of cases of ALS is unknown. Though the uniform incidence of MND throughout the world has been disputed, [5] with the exception of geographical isolates such as on Guam and Guadeloupe, there is remarkably little variation in published studies. This does not immediately favour either an environmental or genetic cause. An apparent increase in incidence in the disorder in the last few decades may be due to improved diagnosis, an aging population, or a genuine increase the frequency of the disease. Specific MNDs are known to be caused by dietary factors in the tropics (konzo in Africa and lathyrism in India). [6,7] Numerous theories have implicated environmental poisons such as pesticides and heavy metals, but epidemiological evidence for this as the cause of typical sporadic ALS is lacking. Rare reports of ALS after electrocution probably represent a genuine biological phenomenon, [8] but this does not seem to provide an insight into the origin of the vast majority of cases. Autoimmune factors have also been explored in some detail. While there is evidence of factors in patient serum that may damage motor neurones in culture, immunomodulation with steroids, intravenous immunoglobulin or plasma exchange has not been shown to be an effective treatment. [9] A viral aetiology is an attractive hypothesis because of the role of an enterovirus in poliomyelitis. Reports of persistent enteroviral RNA in postmortem material from ALS patients continue to occur. [10] As mentioned above, there are a small number of reports of a motor neurone syndrome in HIV positive patients. It is unclear whether this is due to direct viral tropism for motor neurones or an opportunistic infection.

Progressive bulbar palsy, also called progressive bulbar atrophy, involves the brain stem—the bulb-shaped region containing lower motor neurons needed for swallowing, speaking, chewing, and other functions. Symptoms include pharyngeal muscle weakness (involved with swallowing), weak jaw and facial muscles, progressive loss of speech, and tongue muscle atrophy. Limb weakness with both lower and upper motor neuron signs is almost always evident but less prominent. Individuals are at increased risk of choking and aspiration pneumonia, which is caused by the passage of liquids and food through the vocal folds and into the lower airways and lungs. Affected persons have outbursts of laughing or crying (called *emotional lability*). Stroke and myasthenia gravis may have certain symptoms that are similar to those of progressive bulbar palsy and must be ruled out prior to diagnosing this disorder. In about 25 percent of individuals with ALS, early symptoms begin with bulbar involvement. Some 75 percent of individuals with classic ALS eventually show some bulbar

involvement. Many clinicians believe that progressive bulbar palsy by itself, without evidence of abnormalities in the arms or legs, is extremely rare.

Pseudobulbar palsy, which shares many symptoms of progressive bulbar palsy, is characterized by degeneration of upper motor neurons that transmit signals to the lower motor neurons in the brain stem. Affected individuals have progressive loss of the ability to speak, chew, and swallow. Progressive weakness in facial muscles leads to an expressionless face. Individuals may develop a gravelly voice and an increased gag reflex. The tongue may become immobile and unable to protrude from the mouth. Individuals may have outbursts of laughing or crying.

Primary lateral sclerosis (PLS) affects the upper motor neurons of the arms, legs, and face. It occurs when specific nerve cells in the motor regions of the cerebral cortex (the thin layer of cells covering the brain which is responsible for most high-level brain functions) gradually degenerate, causing the movements to be slow and effortful. The disorder often affects the legs first, followed by the body trunk, arms and hands, and, finally, the bulbar muscles. Speech may become slowed and slurred. When affected, the legs and arms become stiff, clumsy, slow and weak, leading to an inability to walk or carry out tasks requiring fine hand coordination. Difficulty with balance may lead to falls. Speech may become slow and slurred. Affected individuals commonly experience pseudobulbar affect and an overactive startle response. PLS is more common in men than in women, with a very gradual onset that generally occurs between ages 40 and 60. The cause is unknown. The symptoms progress gradually over years, leading to progressive stiffness and clumsiness of the affected muscles. PLS is sometimes considered a variant of ALS, but the major difference is the sparing of lower motor neurons, the slow rate of disease progression, and normal lifespan. PLS may be mistaken for spastic paraplegia, a hereditary disorder of the upper motor neurons that causes spasticity in the legs and usually starts in adolescence. Most neurologists follow the affected individual's clinical course for at least 3 to 4 years before making a diagnosis of PLS. The disorder is not fatal but may affect quality of life.

Progressive muscular atrophy is marked by slow but progressive degeneration of only the lower motor neurons. It largely affects men, with onset earlier than in other MNDs. Weakness is typically seen first in the hands and then spreads into the lower body, where it can be severe. Other symptoms may include muscle wasting, clumsy hand movements, fasciculations, and muscle cramps. The trunk muscles and respiration may become affected. Exposure to cold can worsen symptoms. The disease develops into ALS in many instances [11].

Figure-1 is a schematic representation of potential factors in the pathology of MND/ALS. In this model it is presumed that some as yet undefined triggering event acts on a background of susceptibility factors. Most of the molecular and cellular features of the disease for which there is good evidence belong to the series of events which occur downstream of the initiation of motor neurone death.

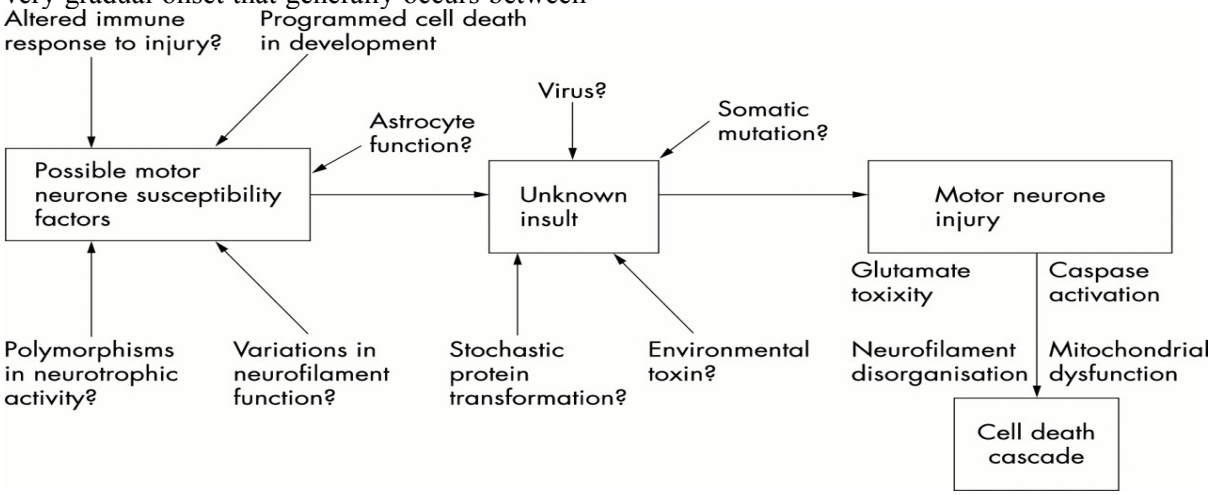


Figure-1: Pathogenesis of MND. Most of what we know about the biological events in the pathogenesis of ALS occur downstream of the initial motor neurone injury. The predisposing factors and the initial trigger to injury are poorly understood.

Spinal muscular atrophy (SMA) is a hereditary disease affecting the lower motor neurons. It is an autosomal recessive disorder caused by defects in the gene SMN1, which makes a protein that is important for the survival of motor neurons (SMN protein). In SMA, insufficient levels of the SMN protein lead to degeneration of the lower motor neurons, producing weakness and wasting of the skeletal muscles. This weakness is often more severe in the trunk and upper leg and arm muscles than in muscles of the hands and feet. SMA in children is classified into three types, based on ages of onset, severity, and progression of symptoms. All three types are caused by defects in the SMN1 gene.

SMA type I, also called *Werdnig-Hoffmann disease*, is evident by the time a child is 6 months old. Symptoms may include hypotonia (severely reduced muscle tone), diminished limb movements, lack of tendon reflexes, fasciculations, tremors, swallowing and feeding difficulties, and impaired breathing [11]. Some children also develop scoliosis (curvature of the spine) or other skeletal abnormalities. Affected children never sit or stand and the vast majority usually die of respiratory failure before the age of 2. However, the survival in individuals with SMA type I have increased in recent years, in relation to the growing trend toward more proactive clinical care.

Symptoms of *SMA type II*, the intermediate form, usually begin between 6 and 18 months of age. Children may be able to sit but are unable to stand or walk unaided, and may have respiratory difficulties. The progression of disease is variable. Life expectancy is reduced but some individuals live into adolescence or young adulthood.

Symptoms of *SMA type III (Kugelberg-Welander disease)* appear between 2 and 17 years of age and include abnormal gait; difficulty running, climbing steps, or rising from a chair; and a fine tremor of the fingers. The lower extremities are most often affected [12]. Complications include scoliosis and joint contractures—chronic shortening of muscles or tendons around joints, caused by abnormal muscle tone and weakness, which prevents the joints from moving freely. Individuals with SMA type III may be prone to respiratory infections, but with care may have a normal lifespan.

Congenital SMA with arthrogryposis (persistent contracture of joints with fixed abnormal posture of the limb) is a rare disorder. Manifestations include severe contractures, scoliosis, chest deformity, respiratory problems, unusually small jaws, and drooping of the upper eyelids.

Kennedy's disease, also known as *progressive spinobulbar muscular atrophy*, is an X-linked recessive disease caused by mutations in the gene for the androgen receptor. Daughters of individuals with Kennedy's disease are carriers and have a 50 percent chance of having a son affected with the disease [13]. The onset of symptoms is variable and the disease may first be recognized between 15 and 60 years of age [12]. Symptoms include weakness and atrophy of the facial, jaw, and tongue muscles, leading to problems with chewing, swallowing, and changes in speech. Early symptoms may include muscle pain and fatigue. Weakness in arm and leg muscles closest to the trunk of the body develops over time, with muscle atrophy and fasciculations. Individuals with Kennedy's disease also develop sensory loss in the feet and hands. Nerve conduction studies confirm that nearly all individuals have a sensory neuropathy (pain from sensory nerve inflammation or degeneration). Affected individuals may have enlargement of the male breasts or develop noninsulin-dependent diabetes mellitus.

The course of the disorder varies but is generally slowly progressive. Individuals tend to remain ambulatory until late in the disease. The life expectancy for individuals with Kennedy disease is usually normal.

Post-polio syndrome (PPS) is a condition that can strike polio survivors decades after their recovery from poliomyelitis. Polio is an acute viral disease that destroys motor neurons. Many people who are affected early in life recover and develop new symptoms many decades later. After acute polio, the surviving motor neurons expand the amount of muscle that each controls. PPS and Post-Polio Muscular Atrophy (PPMA) are thought to occur when the surviving motor neurons are lost in the aging process or through injury or illness. Many scientists believe PPS is latent weakness among muscles previously affected by poliomyelitis and not a new MND. Symptoms include fatigue, slowly progressive muscle weakness, muscle atrophy, fasciculations, cold intolerance, and muscle and joint pain. These symptoms appear most often among muscle groups affected by the initial disease, and may consist of difficulty breathing, swallowing, or sleeping. Other symptoms of PPS may be caused by skeletal deformities such as long-

standing scoliosis that led to chronic changes in the biomechanics of the joints and spine. Symptoms are more frequent among older people and those individuals most severely affected by the earlier disease. Some individuals experience only minor symptoms, while others develop muscle atrophy that may be mistaken for ALS. PPS is not usually life threatening. Doctors estimate that 25 to 50 percent of survivors of paralytic poliomyelitis usually develop PPS.

Motor Neuron Diseases Diagnosed: There are no specific tests to diagnose most MNDs although there are now gene tests for SMA. Symptoms may vary among individuals and, in the early stages of the disease, may be similar to those of other diseases, making diagnosis difficult. A physical exam should be followed by a thorough neurological exam. The neurological exam will assess motor and sensory skills, nerve function, hearing and speech, vision, coordination and balance, mental status, and changes in mood or behavior. Tests to rule out other diseases or to measure muscle involvement may include the following:

Electromyography (EMG) is used to diagnose disorders of lower motor neurons, as well as disorders of muscle and peripheral nerves. In an EMG, a physician inserts a thin needle electrode, attached to a recording instrument, into a muscle to assess the electrical activity during a voluntary contraction and at rest. The electrical activity in the muscle is caused by the lower motor neurons. When motor neurons degenerate, characteristic abnormal electrical signals occur in the muscle. Testing usually lasts about an hour or more, depending on the number of muscles and nerves tested.

EMG is usually done in conjunction with a nerve conduction velocity study. Nerve conduction studies measure the speed and size of the impulses in the nerves from small electrodes taped to the skin. A small pulse of electricity (similar to a jolt from static electricity) is applied to the skin to stimulate the nerve that directs a particular muscle. The second set of electrodes transmits the responding electrical signal to a recording machine. Nerve conduction studies help to differentiate lower motor neuron diseases from peripheral neuropathy and can detect abnormalities in sensory nerves.

Laboratory tests of blood, urine, or other substances can rule out muscle diseases and other disorders that may have symptoms similar to those of MND. For example, analysis of the fluid that surrounds the brain and spinal cord can detect infections or inflammation that can also cause muscle stiffness. Blood tests may be ordered to measure levels of the protein creatine kinase (which is needed for the chemical reactions that produce energy for muscle contractions); high levels may help diagnose muscle diseases such as muscular dystrophy.

Magnetic resonance imaging (MRI) uses a powerful magnetic field to produce detailed images of tissues, organs, bones, nerves, and other body structures. MRI is often used to rule out diseases that affect the head, neck, and spinal cord. MRI images can help diagnose brain and spinal cord tumors, eye disease, inflammation, infection, and vascular irregularities that may lead to stroke. MRI can also detect and monitor inflammatory disorders such as multiple sclerosis and can document brain injury from trauma. Magnetic resonance spectroscopy is a type of MRI scan that measures chemicals in the brain and may be used to evaluate the integrity of the upper motor neurons.

Muscle or nerve biopsy can help confirm nerve disease and nerve regeneration. A small sample of the muscle or nerve is removed under local anesthetic and studied under a microscope. The sample may be removed either surgically, through a slit made in the skin, or by needle biopsy, in which a thin hollow needle is inserted through the skin and into the muscle. A small piece of muscle remains in the hollow needle when it is removed from the body. Although this test can provide valuable information about the degree of damage, it is an invasive procedure and many experts do not believe that a biopsy is always needed for diagnosis.

Transcranial magnetic stimulation was first developed as a diagnostic tool to study areas of the brain related to motor activity. It is also used as a treatment for certain disorders. This noninvasive procedure creates a magnetic pulse inside the brain that evokes motor activity in an area of the body. Electrodes taped to different areas of the body pick up and record the electrical activity in the muscles. Measures of the evoked activity may help in diagnosing upper motor neural dysfunction in MND or monitoring disease progression.

Motor Neuron Diseases Treated: There is no cure or standard treatment for the MNDs. Symptomatic and supportive treatment can help people be more comfortable while maintaining their quality of life. Multidisciplinary clinics, with specialists from neurology, physical therapy, respiratory therapy, and social work are

particularly important in the care of individuals with MNDs.

The drug riluzole (Rilutek®) has been approved by the U.S. Food and Drug Administration (FDA) to treat ALS, prolongs life by 2-3 months but does not relieve symptoms. The drug reduces the body's natural production of the neurotransmitter glutamate, which carries signals to the motor neurons. Scientists believe that too much glutamate can harm motor neurons and inhibit nerve signaling. The FDA has also approved the use of edaravone (Radicava™) to slow the clinicla decline seen in individuals with ALS.

The FDA has approved nusinersen (Spinraza ™) as the first drug approved to treat children and adults with spinal muscular atrophy. The drug is administered by intrathecal injection into the fluid surrounding the spinal cord. It is designed to increase production of the full-length SMN protein, which is critical for the maintenance of motor neurons.

Other medicines may help with symptoms. Muscle relaxants such as baclofen, tizanidine, and the benzodiazepines may reduce spasticity. Botulinum toxin may be used to treat jaw spasms or drooling. Excessive saliva can be treated with amitriptyline, glycopyolate, and atropine or by botulinum injections into the salivary glands. Combinations of dextromethorphan and quinidine have been shown to reduce pseudobulbar affect. Anticonvulsants and nonsteroidal anti-inflammatory drugs may help relieve pain, and antidepressants may be helpful in treating depression. Panic attacks can be treated with benzodiazepines. Some individuals may eventually require stronger medicines such as morphine to cope with musculoskeletal abnormalities or pain, and opiates are used to provide comfort care in terminal stages of the disease.

Physical therapy, occupational therapy, and rehabilitation may help to improve posture, prevent joint immobility, and slow muscle weakness and atrophy. Stretching and strengthening exercises may help reduce spasticity, increase range of motion, and keep circulation flowing. Some individuals require additional therapy for speech, chewing, and swallowing difficulties. Applying heat may relieve muscle pain. Assistive devices such as supports or braces, orthotics, speech synthesizers, and wheelchairs may help some people retain independence.

Proper nutrition and a balanced diet are essential to maintaining weight and strength. People who cannot chew or swallow may require insertion of a feeding tube. In ALS, insertion of a percutaneous gastronomy tube (to help with feeding) is frequently carried out even before it is needed, when the individual is strong enough to undergo this minor surgery. Non-invasive ventilation at night can prevent apnea in sleep, and some individuals may also require assisted ventilation due to muscle weakness in the neck, throat, and chest during daytime.

Prognosis: Prognosis varies depending on the type of MND and the age of onset. Some MNDs, such as PLS or Kennedy's disease, are not fatal and progress slowly. People with SMA may appear to be stable for long periods, but improvement should not be expected. Some MNDs, such as ALS and some forms of SMA, are fatal.

Research is being Done: The mission of the National Institute of Neurological Disorders and Stroke (NINDS) is to seek fundamental knowledge about the brain and nervous system and to use that knowledge to reduce the burden of neurological disease. The NINDS is a component of the National Institutes of Health (NIH), the leading supporter of biomedical research in the world.

The NINDS supports a broad range of research aimed at discovering the cause of MNDs, finding better treatments, and, ultimately, preventing and curing the disorders. Various animal and cellular models are being used to study disease pathology and identify chemical and molecular processes involved with MNDs. Research is focused on creating new and better medicines, developing potential treatments with stem cells, and identifying genetic mutations and other factors that may influence the development of these diseases.

Drug interventions Researchers are testing whether different drugs, agents, or interventions are safe and effective in slowing the progression of MNDs.

SMA occurs when individuals do not have enough SMN protein. NINDS supported researchers are testing drug-like compounds that increase SMN levels to determine if any of them offer potential benefits for treating the disease. If these experiments are successful, researchers will begin testing these compounds in human clinical trials.

One specific class of compounds currently under investigation are anti-sense

oligonucleotides that can either block or correct the processing of RNA molecules, which are the intermediates between genes and proteins. These compounds are a promising strategy for treating familial ALS and SMA, and early-stage clinical testing has shown that these drugs are well tolerated. Additional trials are investigating the therapeutic benefits of these compounds.

NIH is also conducting clinical trials to study drugs to stimulate muscle growth in Kennedy's disease and to suppress endogenous retroviruses in individuals with ALS.

Other compounds and medications, including minocycline, ceftriaxone, dexpramipexole, coenzyme Q10, and lithium, have been tested but were not effective in treating MNDs.

Stem cells Scientists are developing a broad range of model systems in animals and cells to investigate disease processes and expedite the testing of potential therapies. Since stem cells have the ability to develop into many different cell types, including motor neuron and support cells, they could potentially repair the nerve damage caused by MNDs. These strategies have shown promise in mouse models and scientists are currently investigating the safety of using stem cells to treat diseases like ALS in human clinical trials.

As part of these efforts, a large NIH-led collaborative study is investigating the genes and gene activity, proteins, and modifications of adult stem cell models from both healthy people and those with ALS, SMA, and other neurodegenerative diseases to better understand the function of neurons and other support cells and identify candidate therapeutic compounds.

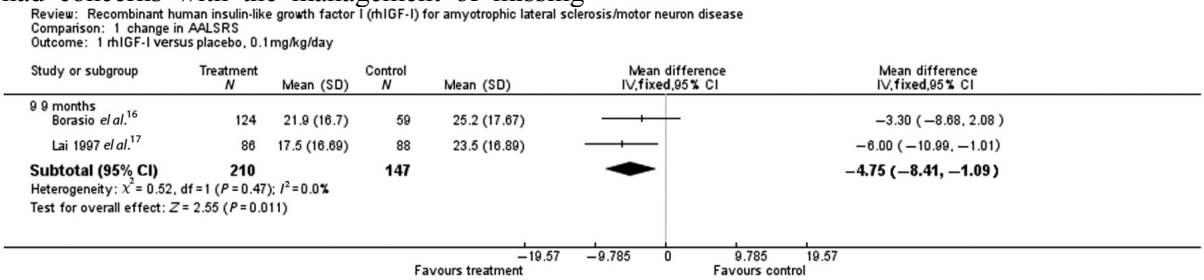
Gene therapies Scientists have used gene therapy to halt motor neuron destruction and slow disease progression in mouse models of SMA and inherited ALS. A small clinical trial of SMN gene replacement therapy is now underway in individuals with SMA. Scientists are using advanced sequencing technologies to identify new gene mutations that are associated with MNDs. These gene discoveries are providing new insights into the cellular disease processes and possible intervention points for therapy.

Antioxidant treatment: Antioxidants have been considered and used for many years as potential treatment of ALS/MND. Many patients still take antioxidants such as vitamin C and vitamin E. Vitamin E at high doses (>1000 mg daily) may increase the risk of haemorrhagic stroke and premature death. Orrell *et al*. [14] identified nine randomized controlled trials. There was insufficient evidence to confirm efficacy of vitamin E 500 mg bd, [15] vitamin E 1 g five times daily, [16] a combination of l-methionine, vitamin E and selenium (Alsemet), [17] or acetylcysteine 50 mg/kg daily subcutaneously.[18] Other antioxidants considered, but with insufficient evidence, include selegiline and dehydroepiandrosterone. A small-molecule antioxidant AEOL-10150 has been under development. Vitamin C and vitamin E are low cost vitamins, usually well tolerated, and continue to be used by some physicians and patients, and there is no clear contraindication, despite lack of proven efficacy.

Ciliary Neurotrophic Growth Factor: Ciliary neurotrophic growth factor (CNTF) is a neurotrophic factor, which was shown to promote motor neuron survival in cell cultures and rodents, including a slowing of disease progression and improvement of muscle strength in the wobbler mouse model of ALS/MND. Bongioanni *et al*.[19] identified two randomized controlled trials, with a total of 1300 patients with ALS/MND. Recombinant CNTF was injected subcutaneously three times a week in the first trial[20] and daily at a lower dose in the second.[21] No significant efficacy was demonstrated, and at higher doses, side effects were observed.

Insulin-like growth factor: Insulin-like growth factor I (IGF-I) is a naturally occurring peptide with neurotrophic effects. Beneficial changes have been reported in a number of ALS/MND and other neuropathy models, including G93A SOD1 transgenic mice. Mitchell *et al*.[22] identified two randomized controlled trials suitable for inclusion. Using subcutaneous recombinant human IGF-I (rhIGF-I) daily, in a European trial with 124 receiving rhIGF-I 0.1 mg/kg/day and 59 placebo, no significant change in the Appel ALS Rating Scale (AALSRS) score was found at 9 months treatment.[23] In a North American trial with 89 receiving rhIGF-I 0.05 mg/kg/day, 87 receiving 0.1 mg/kg/day and 90 placebo, there was a significant benefit on change in AALSRS score at 9 months.[24] The combined analysis of both trials showed a significant benefit on change in AALSRS score in the treated group (Fig. 3). Mitchell *et al*.[22] concluded that the available trials do not allow a definitive assessment of the clinical efficacy of rhIGF-I in ALS/MND. Mitchell *et al*. had concerns including small sample sizes, short study duration and choice of AALSRS as a

source of primary efficacy measure. They also had concerns with the management of missing data and other risks of bias.[22]



A meta-analysis of change in AALSRS, comparing treatment with rhIGF-I 0.1 mg/day versus placebo, of ALS/MND patients for 9 months, for two studies described in the text. A benefit of rhIGF-I is demonstrated. Mitchell et al.,[15] *copyright Cochrane Collaboration, reproduced with permission.*

Source: https://academic.oup.com/view-large/figure/4071356/ldp04903.jpeg

A third randomized controlled trial from the USA has recently been published (and not yet included in the Cochrane review). Patients with ALS received 0.05 mg/kg rhIGF-I subcutaneously twice daily, or placebo, for 2 years. There was no benefit on change in manual muscle score, survival or rate of change of ALSFRSR.[25] Variants of IGF-I are also recognized, with potential benefits including altered specificity and the possibility of improved modes of administration.[26]

Conclusion: The anterior horn cells control all voluntary movement: motor activity, respiratory, speech, and swallowing functions are dependent upon signals from the anterior horn cells. Diseases that damage the anterior horn cells, therefore, have a profound impact. Symptoms of anterior horn cell loss (weakness, falling, choking) lead patients to seek medical attention. Neurologists are the most likely practitioners to recognize and diagnose damage or loss of anterior horn cells. ALS, the prototypical motor neuron disease, demonstrates the impact of this class of disorders. ALS and other motor neuron diseases can represent diagnostic challenges. Neurologists are often called upon to serve as a "medical home" for these patients: coordinating care, arranging for durable medical equipment, and leading discussions about end-of-life care with patients and caregivers. It is important for neurologists to be able to identify motor neuron diseases and to evaluate and treat patients affected by them.

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