Motor Neuron Diseases

U.S. DEPARTMENT OF HEALTH
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What are motor neuron diseases?

The motor neuron diseases (MNDs) are a group of progressive neurological disorders that destroy motor neurons, the cells that control skeletal muscle activity such as walking, breathing, speaking, and swallowing. This group includes diseases such as amyotrophic lateral sclerosis, progressive bulbar palsy, primary lateral sclerosis, progressive muscular atrophy, spinal muscular atrophy, Kennedy's disease, and post-polio syndrome.

Normally, messages or signals from nerve cells in the brain (upper motor neurons) are transmitted to nerve cells in the brain stem and spinal cord (lower motor neurons) and from them to muscles in the body. Upper motor neurons direct the lower motor neurons to produce muscle movements.

When the muscles cannot receive signals from the lower motor neurons, they begin to weaken and shrink in size (muscle atrophy or wasting). The muscles may also start to spontaneously twitch. These twitches (fasciculations) can be seen and felt below the surface of the skin.

When the lower motor neurons cannot receive signals from the upper motor neurons, it can cause muscle stiffness (spasticity) and overactive reflexes. This can make voluntary movements slow and difficult. Over time, individuals with

MNDs may lose the ability to walk or control other movements.

How are they classified?

MNDs are classified according to whether the loss of function (degeneration)

- is inherited (passed down through family genetics)
- is sporadic (no family history)
- affects the upper motor neurons, lower motor neurons, or both

In cases where a motor neuron disease is inherited, it is usually caused by mutations in a single gene. These conditions are usually inherited in one of several patterns:

- **Autosomal dominant** means that a person needs to inherit only one copy of the defective gene from one parent with the disorder to be at risk of the disease. There is a 50 percent chance that a child of an affected person will inherit the abnormal gene and develop the disease.
- **Autosomal recessive** means a person must inherit a copy of the defective gene from each parent. 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 (e.g., siblings).
- **X-linked inheritance** occurs when the mother carries the defective gene on one of her X chromosomes and passes the disorder along to her sons. Boys inherit an X chromosome from their mother and a Y chromosome from their father. Sons have

a 50 percent risk of inheriting the abnormal X chromosome and developing the disease. Girls 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 usually makes them asymptomatic carriers of the mutation.

Who is at risk?

MNDs occur in both adults and children. In children, MNDs are typically due to specific gene mutations, as in spinal muscular atrophy. Symptoms can be present at birth or appear in early childhood. In adults, MNDs are more likely to be sporadic, meaning the disease occurs with no family history. Symptoms typically appear after age 50, though onset of disease may occur at any age.

What causes motor neuron diseases?

Some MNDs are inherited, but the causes of most MNDs are not known. In sporadic or non-inherited MNDs, environmental, toxic, viral, and/or genetic factors may play a role in the development of the disease.

What are the symptoms of motor neuron diseases?

Though there are several different types of MNDs, they all cause muscle weakness that gradually worsens over time and leads to disability. In some cases, these diseases are fatal. Some of the most common MNDs include:

Amyotrophic lateral sclerosis (ALS), also called classical motor neuron disease, affects

both the upper and lower motor neurons. It causes rapid loss of muscle control and eventual paralysis. Many doctors use the term motor neuron disease and ALS interchangeably.

Early symptoms of ALS usually include muscle weakness or stiffness in a limb or muscles of the mouth or throat (so-called bulbar muscles). Gradually almost all the muscles under voluntary control are affected, and individuals lose their strength and the ability to speak, eat, move, and even breathe. Most people with ALS die from respiratory failure, usually within 3 to 5 years from the onset of symptoms. However, about 10 percent of people with ALS 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 slightly more often than women. Most cases of ALS (about 90 percent) are considered sporadic, and family members of those individuals are not at increased risk of developing the disease.

About 10 percent of ALS cases are familial, with mutations in more than 15 disease-causing genes. Most of the gene mutations discovered account for a very small number of cases. The most common familial form of ALS in adults is caused by a defect in a gene known as "chromosome 9 open reading frame 72," or *C9ORF72,* which accounts for 25 to 40 percent of familial ALS in the United States. The function of this gene is still unknown.

About 10 to 12 percent of familial cases result from mutations in the gene that encodes the

enzyme copper-zinc superoxide dismutase 1 (*SOD1*). There are also rare juvenile-onset forms of familial ALS.

Progressive bulbar palsy (PBP), also called progressive bulbar atrophy, attacks the lower motor neurons connected to the brain stem. The brain stem (also known as the bulbar region) controls the muscles needed for swallowing, speaking, chewing, and other functions.

Many ALS experts consider PBP within the spectrum of ALS because the majority of individuals who begin with this form of the disease eventually develop more widespread MND. Indeed, many clinicians believe that PBP by itself, without evidence of abnormalities in the arms or legs, is extremely rare.

Symptoms, which worsen over time, include trouble chewing, speaking, and swallowing. Individuals may also have weakness in their tongue and facial muscles, twitches, and a reduced gag reflex. They may also experience weakness in their arms or legs, but it is less noticeable than other symptoms.

Because they have difficulty swallowing, individuals are at risk of choking and inhaling food and saliva into the lungs. People can also have emotional changes and may begin to laugh or cry at inappropriate times (called pseudobulbar affect or emotional lability). Some symptoms of stroke and myasthenia gravis are similar to those of progressive bulbar palsy and must be ruled out prior to diagnosis.

In about one-third of individuals with ALS, early symptoms begin with the bulbar muscles. Some 75 percent of individuals with classic ALS

eventually show some problems swallowing, speaking, and chewing.

Primary lateral sclerosis (PLS) affects only the upper motor neurons, causing the movements in the arms, legs, and face to be slow and difficult. The disorder often affects the legs first, followed by the torso, arms and hands, and, finally, the muscles used for swallowing, speaking, and chewing.

The legs and arms become stiff, clumsy, slow, and weak, making it difficult to walk or carry out tasks requiring fine hand coordination. Speech may become slowed and slurred. Individuals may have difficultly balancing, increasing the risk of falls. Affected individuals may also experience emotional changes and become easily startled.

Like ALS, PLS most often occurs in midlife. It is more common in men than in women. The cause of PLS is unknown.

PLS is sometimes considered a variant of ALS, but it progresses much more slowly than ALS and is not fatal. A significant proportion of those with PLS will develop lower motor neuron disease, changing the diagnosis to ALS. Because of this, most neurologists monitor an individual for at least 4 years before making a diagnosis of PLS.

Progressive muscular atrophy (PMA) is a rare disease marked by slow but progressive damage to only the lower motor neurons. It largely affects men, and usually at a younger age than most other adult-onset 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 (shrinking), clumsy hand movements, twitches, and muscle cramps. The torso muscles and breathing may become affected. Exposure to cold can worsen symptoms. A diagnosis can turn out to be slowly progressive ALS, in some cases.

Spinal muscular atrophy (SMA) is an inherited disease that affects lower motor neurons. It is the most common genetic cause of infant mortality. Defects in the *SMN1* gene result in a loss of the SMN protein. Low levels of the SMN protein cause lower motor neurons to deteriorate, producing muscle weakness and wasting. This weakness is often worse in the proximal muscles, which are closer to the center of the body (e.g., torso, thigh, and arm), than distal muscles which are further away (e.g., hands and feet).

SMA is classified into three main types—based on age of onset, severity, and progression of symptoms. Generally, the earlier symptoms start to appear, the greater the impact on motor function. All three main 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 poor muscle tone, lack of reflexes and motor development, twitching, tremors, and difficulties swallowing, chewing, and breathing. Some children also develop scoliosis (curvature of the spine) or other skeletal abnormalities. These children never sit independently and, before the availability of genetic therapies, most died by 1 year of age.

- **SMA type II** usually begins to appear between ages 6 and 18 months. Children may be able to sit but cannot stand or walk without help and may have difficulty breathing.
- **SMA type III** (Kugelberg-Welander disease) usually appears between 2 and 17 years of age, with symptoms that include abnormal gait (e.g., problems walking); difficulty running, climbing steps, or rising from a chair; and a slight tremor in the fingers. The lower limbs are most often affected. Complications include scoliosis and chronic shortening of muscles or tendons around the joints (contractures), which prevents the joints from moving freely. Individuals with SMA type III may be prone to respiratory infections.

SMARD1, or spinal muscular atrophy with respiratory distress type 1, is a rare, genetically distinct form of SMA. The disorder is caused by mutations in the *IGHMBP2* (immunoglobulin helicase μ-binding protein 2) gene. Symptoms appear during infancy, between ages 6 weeks and 6 months. Children with SMARD1 suddenly may be unable to breathe due to diaphragm paralysis and may develop weakness in their distal muscles.

Congenital SMA with arthrogryposis is a rare disorder that appears at birth. Symptoms include severe muscle contractures, making babies unable to extend or flex the affected joints. In the majority of cases, both the arms and legs are affected. Other symptoms include scoliosis, chest deformity, respiratory problems, unusually small jaws, and drooping of the eyelids.

Kennedy's disease (spinal and bulbar muscular atrophy, bulbo-spinal muscular atrophy, X-linked spinal and bulbar muscular atrophy) is an X-linked recessive disease that affects men. It is 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.

The onset of symptoms varies but most commonly the disease is first recognized between 20 and 40 years of age. Generally, the disease progresses very slowly. Early symptoms may include tremor of outstretched hands, muscle cramps during physical activity, and muscle twitches. Individuals also may have weakness of the facial, jaw, and tongue muscles, leading to problems with chewing, swallowing, and speaking.

Over time, individuals develop weakness in the arms and legs, often beginning in the pelvic or shoulder regions. They also may develop pain and numbness in the hands and feet. However, individuals tend to retain the ability to walk until the later stages of the disease, and many have a normal lifespan.

Post-polio syndrome (PPS) can strike polio survivors decades (some 30 to 40 years) after they have recovered from the initial illness, which can cause major damage to motor neurons. Symptoms include fatigue, muscle and joint weakness, and pain that slowly gets worse over time, muscle atrophy and twitches, and decreased tolerance to cold. These symptoms appear most often among muscle groups affected by the initial polio illness. Other symptoms include difficulty breathing, swallowing, or sleeping.

Older people and those individuals most severely affected by the earlier disease are more likely to experience symptoms. Some individuals experience only minor symptoms, while others develop muscle atrophy that may be mistaken for ALS. PPS is usually not life-threatening. Doctors estimate that 25 to 50 percent of survivors of polio generally develop PPS.

Respiratory insufficiency, a condition in which the lungs cannot properly take in oxygen or expel carbon dioxide, is a feature of most MNDs. Symptoms may include breathlessness, shortness of breath that occurs while lying down, recurrent chest infections, disturbed sleep, poor concentration and/or memory, confusion, morning headaches, and fatigue.

How are motor neuron diseases diagnosed?

In many cases, there are no specific tests to diagnose MNDs. Symptoms may vary among individuals and, in the early stages, may be similar to those of other diseases, making diagnosis difficult. However, there are gene tests for SMA, Kennedy's disease, and some causes of familial ALS.

A physical exam should be followed by an extensive neurological exam. The exam assesses motor and sensory skills, nerve function, hearing and speech, vision, coordination and balance, mental status, and changes in mood or behavior.

The following two tests, which may be considered an extension of the neurological examination, are the most important. These tests, usually done together, can identify the differences between muscles diseases and MNDs.

- **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 movement and at rest. The electrical activity in the muscle is triggered by the lower motor neurons. When motor neurons are damaged, abnormal electrical signals occur in the muscle. Testing usually lasts about an hour or more, depending on the number of muscles and nerves tested.
- **A nerve conduction study** is usually done in combination with an EMG. 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 electrical response to a recording machine. Nerve conduction studies help to differentiate lower motor neuron diseases from peripheral neuropathy and can detect abnormalities in sensory nerves.

Additional tests to rule out other diseases or to measure muscle involvement may include the following:

- **Laboratory tests** of blood, urine, or other substances can rule out muscle diseases and other disorders that may have symptoms similar to MNDs. For example, analysis of the fluid that surrounds the brain and spinal cord can detect infections or inflammation that also can 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 and a computer to produce detailed images of tissues, organs, bones, nerves, and other body structures. 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. It is often used to rule out diseases that affect the head, neck, and spinal cord. 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 anesthesia 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 needed to diagnose MND.

How are motor neuron diseases treated?

There is no cure or standard treatment for MNDs. Symptomatic and supportive treatment can help people affected by these diseases 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.

Medication

- **Riluzole.** Riluzole is the first drug approved by the U.S. Food and Drug Administration (FDA) to treat ALS. In clinical trials, people taking riluzole lived about 10 percent longer when compared to those not taking the drug. However, riluzole cannot reverse the damage already done to motor neurons. Although it is not fully understood how the drug works, riluzole has been shown to reduce the release of glutamate and to block sodium channels. Both of these actions may provide protection against damage to motor neurons.
- **Edaravone.** In 2017, the FDA approved the drug edaravone to treat ALS. Edaravone, an antioxidant, slows down the decline of physical function and prevents disease progression in people with ALS. However, the drug, which is administrated intravenously, cannot restore function.
- **Nusinersen.** In 2016, the FDA approved the first drug to treat children and adults with SMA. Nusinersen, an injection medication, is a type of treatment called anti-sense

oligonucleotide therapy and works by increasing the SMN protein necessary for the muscles and nerves to work normally.

- **Onasemnogeme abeparovec-xioi**. In May 2019, the FDA approved onasemnogene abeparovec-xioi (Zolgensma ™) gene therapy for children less than 2 years old who have infantile-onset SMA. A safe virus delivers a fully functional human SMN gene to the targeted motor neurons, which in turn improves muscle movement and function, and also improves survival.
- **Muscle relaxers.** Drugs such as baclofen, tizanidine, and the benzodiazepines may reduce muscle stiffness and help muscle spasms.
- **Botulinum toxin**. Injections of botulinum toxin may be used to treat muscle stiffness by weakening overactive muscles. They also may be injected into the salivary glands to stop drooling. Excessive saliva also can be treated with medications such as amitriptyline, glycopyrrolate, and atropine.

Supportive therapies

- **Physical therapy and rehabilitation**. These therapies may help improve posture, prevent joint immobility, and slow muscle weakness and atrophy. Stretching and strengthening exercises may help reduce stiffness, as well as increase range of motion and circulation. 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 maintain independence.

- **Proper nutrition and a balanced diet.** These things are essential to maintaining weight and strength. People who cannot chew or swallow may require a feeding tube.
- **Ventilators**. Non-invasive positive pressure ventilation (NIPPV) at night can prevent sleep apnea. Some individuals may also require assisted ventilation during the day due to muscle weakness in the neck, throat, and chest.

What is the prognosis?

Prognosis varies depending on the type of MND and the age of symptom onset. MNDs, such as PLS or Kennedy's disease, are usually not fatal and progress slowly. People with SMA type III may be stable for long periods. Some forms of MND, such as the severe form of SMA and ALS, are fatal.

What 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. NINDS is a component of the National Institutes of Health (NIH), the leading supporter of biomedical research in the world.

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 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 intermediaries between genes and proteins. These compounds are a promising strategy for treating familial ALS and other NMDs. In 2016, FDA approved nusinersen—an anti-sense oligonucleotide therapy—for the treatment of SMA.

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 support cells and identify candidate therapeutic compounds.

In other studies, scientists are investigating human spinal cord-derived stem cells to discover if these cells can help improve function in people with ALS. Researchers also are studying autologous mesenchymal stem cells secreting neurotrophic factors (MSC-NTF) as treatment for ALS. MSC-NTF are made from a person's own bone marrow cells and then injected into the cerebrospinal fluid.

Gene therapy

Scientists are testing the potential of gene therapy to halt motor neuron destruction and slow disease progression in animal models of SMA and inherited ALS. Small clinical trials of SMN gene replacement therapy are now underway in individuals with SMA. Other gene therapy trials are studying familial ALS.

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.

Where can I get more information?

For more information on neurological disorders or research programs funded by NINDS, contact the Institute's Brain Resources and Information Network (BRAIN) at:

BRAIN
P.O. Box 5801
Bethesda, MD 20824
800-352-9424
www.ninds.nih.gov

More information about MND research supported by NINDS and other NIH Institutes and Centers can be found using NIH RePORTER (projectreporter.nih.gov), a searchable database of current and past research projects supported by NIH and other federal agencies. RePORTER also includes links to publications and resources from these projects.

Additional information on motor neuron diseases is available from the following organizations:

ALS Association
1275 K Street, NW, Suite 250
Washington, DC 20005
202-407-8580
800-782-4747
www.alsa.org

ALS Therapy Development Institute
300 Technology Square, Suite 400
Cambridge, MA 02139
617-441-7200
www.als.net

Cure SMA
925 Busse Road
Elk Grove Village, IL 60007
800-886-1762
www.curesma.org

Kennedy's Disease Association
P.O. Box 1105
Coarsegold, CA 93614
855-532-7762
www.kennedysdisease.org

Les Turner ALS Foundation
5550 W. Touhy Avenue, Suite 302
Skokie, IL 60077
847-679-3311
www.lesturnerals.org

Muscular Dystrophy Association
161 N. Clark, Suite 3550
Chicago, IL 60601
800-572-1717
www.mda.org

Post-Polio Health International
4207 Lindell Boulevard, Suite 110
St. Louis, MO 63108
314-534-0475
www.post-polio.org

Project ALS
801 Riverside Drive, Suite 6G
New York, NY 10032
212-420-7382
855-900-2257
www.projectals.org

Spastic Paraplegia Foundation
1605 Goularte Place
Fremont, CA 94539
877-773-4483
www.sp-foundation.org

Spinal Muscular Atrophy Foundation
126 East 56th Street, 30th Floor
New York, NY 10022
646-253-7100
www.smafoundation.org

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