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Amyotrophic Lateral Sclerosis: III. Differential Diagnosis

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Abstract

Amyotrophic lateral sclerosis is a progressive neurodegenerative disease that primarily affects motor neurons in the brain and spinal cord, leading to muscle weakness, atrophy, eventual paralysis, and ultimately respiratory failure and death. It must be differentiated from the "ALS-mimic syndromes", which are unrelated disorders that may have a similar presentation and clinical features to ALS or its variants. Because symptoms of ALS can be like those of a wide variety of other more treatable diseases or disorders, appropriate tests must be conducted to exclude the possibility of other conditions.

This article describes the several diagnostic tests and procedures available for reaching a differential diagnosis of ALS. It also discusses a few ALS-mimic diseases including Lambert–Eaton myasthenic syndrome, multifocal motor neuropathy, and spinal muscular atrophy.

Abbreviations

AD: Alzheimer's disease; ALS: Amyotrophic lateral sclerosis; ALS-RC: ALS Research Collaborative; ALS-TDI: ALS Therapy Development Institute; ANS: Autonomous nervous system; ASD: Autism-spectrum disorder; BD: Batten's disease; BD: Bipolar disorder; BFS: Benign fasciculation syndrome; BMA: Bulbar muscular atrophy; CFS: Cramp fasciculation syndrome; CJD: Creutzfeldt-Jakob disease; CNS: central nervous system; CP: Cerebral palsy; CS: Cervical spondylosis; CT: Clinical trial; EHIV: Human immunodeficiency virus; EMG: Electromyography; fALS: familial ALS; GBS: Guillain-Barre syndrome; HD: Huntington's disease; HIV: Human immunodeficiency virus; HTLV: Human T-lymphotropic virus; IVIg: Intravenous immunoglobulin; LD: Lyme disease; LEMS: Lambert-Eaton myasthenic syndrome; LMN: Lower motor neurons; MD: Muscular dystrophy; MFMN: Multifocal motor neuropathy; MG: Myasthenia gravis; MMA: Monomelic atrophy; MMN: Multifocal motor

neuropathy; MRI: Magnetic resonance imaging; MS: Multiple sclerosis; MSA: Multiple system atrophy; NCV: Nerve conduction velocity; nEMG: needle EMG; PD: Parkinson's disease; PLS: Primary lateral sclerosis; PNP: Peripheral neuropathy; PPS: Post-polio syndrome; PrBP: Progressive bulbar palsy; PrMA: Progressive muscular atrophy; PsBP: Pseudobulbar palsy; SB: Spina bifida; SCLC: Small-cell lung carcinoma; SMA: Spinal muscular atrophy; SOD: Sodium dismutase; UMN: Upper motor neurons; VGCC: Voltage-gated calcium channels.

Keywords

Amyotrophic lateral sclerosis; bulbar muscular atrophy; Lambert-Eaton myasthenic syndrome; multifocal motor neuropathy; monomelic atrophy; progressive bulbar palsy; progressive muscular atrophy; pseudobulbar palsy; spinal muscular atrophy.

Introduction

Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disease that primarily affects motor neurons in the brain and spinal cord, leading to muscle weakness, atrophy, eventual paralysis, and ultimately respiratory failure and death. Several infectious diseases can sometimes cause ALS-like symptoms, including human immunodeficiency virus (HIV), human T-lymphotropic virus (HTLV), Lyme disease (LD), and syphilis. Neurological disorders such as multiple sclerosis (MS), post-polio syndrome (PPS), multifocal motor neuropathy (MFMN), spinal muscular atrophy (SMA), and bulbar muscular atrophy (BMA) can also mimic certain aspects of the disease and should be considered. Because symptoms of ALS can be like this wide variety of other, more treatable diseases or disorders, appropriate tests must be conducted to exclude the possibility of other conditions. Some of these several confusing factors will be succinctly presented in a sidebar.

ALS must also be differentiated from "ALS-mimic syndromes", which are unrelated disorders that may have similar presentation and clinical features to ALS or its variants. Disorders of the neuromuscular function, such as, myasthenia gravis (MG), Lambert-Eaton myasthenic syndrome (LEMS), may also mimic ALS, although this rarely presents diagnostic difficulty over time.

Because the prognosis of ALS and closely related subtypes of motor neuron disease are generally poor, neurologists may carry out investigations to evaluate and exclude other diagnostic possibilities.

A brief history of ALS diagnosis

In the 1950s, electromyography (EMG) and nerve conduction velocity (NCV) testing began to be used to evaluate clinically suspected ALS. In 1969, Edward H. Lambert published the first EMG/NCS diagnostic criteria for ALS, consisting of four findings he considered strongly support the diagnosis. Since then, several diagnostic criteria have been developed, which are mostly in use in clinical trials (CT) for inclusion/exclusion criteria research purposes and to stratify patients for analysis. Research diagnostic criteria for ALS include the "El Escorial" (1994, revised in 1998), the "Awaji" criteria (2006) proposed using EMG and NCV tests to help diagnose ALS earlier, and most recently the "Gold Coast" criteria (2019).

However, no single test can provide a definite diagnosis of ALS. Instead, the diagnosis is primarily made based on a physician's clinical assessment after ruling out other diseases. Physicians often obtain the person's full medical history and conduct neurologic examinations at regular intervals to assess whether signs and symptoms such as muscle weakness, muscle atrophy, hyperreflexia, Babinski's sign, and spasticity are worsening. Many biomarkers are being studied for the condition, but as of 2023 are not in general medical use.

On the diagnosis

Diagnosing ALS is usually straightforward if the patient has progressive, generalized symptoms in the bulbar and limb regions. Diagnosis early in the course of the disease when the patient has symptoms limited to one or two regions (bulbar, upper limb, trunk, lower limb) may be difficult and depends on the presence of signs in other regions and supportive findings in ancillary investigations. The mean time from the onset of symptoms to confirmation of the diagnosis of ALS is 10–18 months. Delays may arise if early or intermittent symptoms are unrecognized or denied by the patient, or because of inefficient referral pathways to a neurologist.

There are cogent reasons for making the diagnosis as early as possible. Psychologically, the absence of a definitive diagnosis, even of a disorder carrying a poor prognosis, causes distress and anxiety. Early diagnosis may obviate onerous and potentially expensive tours of the healthcare system and facilitate future planning. It may also provide opportunities for treatment with neuroprotective agents at a time when fewer cells are irreversibly compromised. Studies in experimental animal models and humans with SOD1 (sodium dismutase 1) gene mutations indicate that the loss of motor neurons is preceded by a period of cellular dysfunction which may be reversible.

The Differential Diagnosis

Because symptoms of ALS can be like those of a wide variety of other, more treatable diseases or disorders, appropriate tests must be conducted to exclude the possibility of these other conditions. One of these tests is electromyography (EMG), a special recording technique that detects electrical activity in muscles. Certain EMG findings can support the diagnosis of ALS. Another common test measures nerve conduction velocity (NCV). Specific abnormalities in the NCV results may suggest, for example, that the person has a form of peripheral neuropathy (PNP) - damage to peripheral nerves, or myopathy (muscle disease) rather than ALS. While a magnetic resonance imaging test (MRI) is often normal in people with early-stage ALS, it can reveal evidence of other problems that may be causing the symptoms.

Based on the person's symptoms and findings from the examination and from these tests, the physician may order tests on blood and urine samples to eliminate the possibility of other diseases, as well as routine laboratory tests. In some cases, for example, if a physician suspects the person may have a myopathy rather than ALS, a muscle biopsy may be performed.

ALS must particularly be differentiated from the "ALS mimic syndromes", which are unrelated disorders that may have a similar presentation and clinical features to ALS or its variants. Because the prognosis of ALS and closely related subtypes of motor neuron disease are generally poor, neurologists may carry out investigations to evaluate and exclude other diagnostic possibilities. Disorders of the neuromuscular junction, such as myasthenia gravis (MG) and Lambert–Eaton myasthenic syndrome (LEMS), may also mimic ALS, although this rarely presents diagnostic difficulty over time. Benign fasciculation syndrome (BFS) and cramp fasciculation syndrome (CFS) may also, occasionally, mimic some of the early symptoms of ALS. Nonetheless, the absence of other neurological features that develop inexorably with ALS means that, over time, the distinction will not present any difficulty to the experienced neurologist. Where doubt remains, EMG may be helpful.

Diagnostic Tests and Procedures

The journey from the first symptoms of ALS to a confirmed diagnosis can be long and challenging. There is no one test that can determine whether someone does

or does not have ALS. Many kinds of testing are often required to rule out the various other diseases that can cause similar symptoms – from cancers to autoimmune disorders to other neurodegenerative diseases like Parkinson's disease (PD) and multiple sclerosis (MS).

The diagnosis process can take months, or even years. However, obtaining a conclusive diagnosis of ALS is crucially important for developing a proper plan for care and treatment. It is also often a requirement if one is interested in participating in a clinical trial.

The most widely accepted benchmarks for assessing whether a person has ALS are known as the "El Escorial" criteria. According to these criteria, to receive a diagnosis of ALS, three types of evidence or lack thereof must be present:

• **Evidence of degeneration:** First, the patient must display evidence of degeneration of BOTH the upper and lower motor neurons. Evidence must be provided by clinical, electrophysiological or neuropathologic examination.

• **Evidence of worsening symptoms:** Second, there must be evidence that the person's symptoms are worsening in one part of the body and/or spreading to other parts. Alternatively, progressive spread of symptoms or signs within a region or to other regions, as determined by history or examination.

• **Lack of evidence of other symptoms:** Third, there must be an observed lack of evidence that these symptoms are caused by another disease.

Throughout the diagnostic process, people might receive a diagnosis of "suspected", "possible", "probable" or "definite"ALS, depending on the evidence observed by clinicians. Without a definite diagnosis, people with possible or probable ALS nevertheless remain eligible to participate in a growing number of clinical trials evaluating emerging treatments for the disease.

Neurological tests

When someone begins to experience the early symptoms of ALS, like muscle weakness in the limbs or face, the first step is often an appointment with a neurologist. In this examination, the neurologist will most likely ask questions about the person experiencing ALS-like symptoms, family history, work, and possible environmental risk factors. They will also look for signs of localized muscle weakness, upper and lower motor neuron symptoms like involuntary twitching, hyperactive reflexes, and muscle spasticity.

Electromyography tests

If a neurologist suspects the cause of a person's symptoms to be ALS, electromyography (or EMG testing) is often the next step in the diagnostic process. These tests enable clinicians to determine whether motor nerves are plugged into the muscles and are working properly. An EMG tests the ability of muscles to contract in response to the electrical stimuli from the nerves. First, electric shocks are sent through the nerves, to determine whether the symptoms are a result of nerve damage or another disease that affects the nerves such as multifocal motor neuropathy (MFMN). This part of an EMG test is also known as a "nerve conduction study (NCS).

In the second part of an EMG test, also known as "needle electromyography" (nEMG), fine needles are inserted into certain muscles to observe the electrical activity both at rest and when the test subject tries to move. Abnormalities observed during this test may provide evidence that ALS is in fact behind a person's symptoms. Some people may need multiple EMG tests before they receive an ALS diagnosis, as the test may not be able to clearly identify the signs of ALS early on in a person's progression.

Nerve conduction velocity tests

Nerve conduction velocity studies (NCV) test whether the motor nerves can send signals of sufficient strength to enable movement of the muscles whereas EMG tests measure the ability of these muscles to trigger contraction in response to these signals.

Specific abnormalities in the NCV results may suggest, for example, that the person has a form of peripheral neuropathy or myopathy rather than ALS.

Imaging tests

A magnetic resonance imaging (MRI) test may also be necessary during the ALS diagnosis process. An MRI is a non-invasive procedure that allows doctors to see detailed images of organs and tissues inside the body. It enables clinicians to examine organs and tissues including the brain and spinal cord. It can help rule out several other possible causes of ALS-like symptoms such as brain tumors, MS, and certain disorders of the spinal cord, a herniated disk in the neck, syringomyelia, or cervical spondylosis (CS).

Laboratory tests

Based on the person's symptoms and findings from the examination and from the above tests, and to further rule out other diseases, the physician may order tests on blood and urine samples, and even a spinal tap to eliminate the possibility of other diseases and rule out infections with similar symptoms, such as LD.

Muscle biopsies

Clinicians may also recommend a muscle biopsy to further investigate affected muscles. In this procedure, a small piece of muscle is removed and examined under the microscope. Such examinations under a microscope can help rule out certain muscle diseases.

Genetic tests

When a familial ALS (fALS) is suspected, genetic testing might also be recommended. After receiving an ALS diagnosis, one may also choose to undergo genetic testing. This can help determine whether an individual's ALS case is sporadic, or if it is caused by an inherited gene mutation. This can be very important for people who have a family history of the disease.

Commercially available tests can identify dozens of ALS-related genes. Those who undergo genetic testing are typically provided genetic counseling during which they learn how to interpret results. Determining what mutations might be present can also determine whether someone might be eligible for certain clinical trials for drugs targeted at specific mutations, such as C9orf72 or SOD1.

Future tests

In addition to the tests available today, researchers are working to develop new, more accurate, and faster tests to diagnose ALS. At the ALS Therapy Development Institute (ALS TDI), a major goal of its ALS Research Collaborative (ALS RC) is to identify new ways to more quickly and accurately diagnose ALS. Through an in-home blood collection program, they are searching for biological indicators (biomarkers) that can be detected through a simple blood test. Finding more reliable biomarkers of ALS progression or risk could potentially give clinicians new tools to diagnose the disease or even identify people who are at high risk of developing ALS before they show symptoms. Other scientists are developing a new method called "electrical impedance myography" (EIM) to diagnose ALS. This test helps identify changes in affected muscles, including atrophy. Scientists hope that this tool might also predict the spread of ALS and aid in the development of treatments for the disease.

Conclusions and Take-Aways

- Several infectious diseases can sometimes cause ALS-like symptoms, including human immunodeficiency virus, human T-lymphotropic virus, Lyme disease, and syphilis. Neurological disorders such as multiple sclerosis, post-polio syndrome, multifocal motor neuropathy, spinal muscular atrophy, and bulbar muscular atrophy can also mimic certain aspects of the disease and should be considered.

- ALS must be differentiated from the "ALS-mimic syndromes", which are unrelated disorders that may have a similar presentation and clinical features to ALS or its variants. Because the prognosis of ALS and closely related subtypes of motor neuron disease are generally poor, neurologists may carry out investigations to evaluate and exclude other diagnostic possibilities.

- Because symptoms of ALS can be like those of a wide variety of other, more treatable diseases or disorders, appropriate tests must be conducted to exclude the possibility of other conditions.

- ALS must be differentiated from the "ALS-mimic syndromes", which are unrelated disorders that may have a similar presentation and clinical features to ALS or its variants.

- Diagnostic tests include electromyography, nerve conduction velocity, imaging, laboratory tests, muscle biopsies, and genetic tests.

- In a Sidebar, a few ALS-mimic syndromes are reviewed including Lambert–Eaton myasthenic syndrome, multifocal motor neuropathy, and spinal muscular atrophy.

ALS mimic syndromes are unrelated disorders that may have a similar presentation and clinical features to ALS or its variants (Table 1):

Motor neuron diseases	**Nervous system diseases**	**Neurodegenerative diseases**
1.Amyotrophic lateral sclerosis (ALS)	1.**Alzheimer's disease (AD)**	1. **Alzheimer's disease (AD)**
2.Primary lateral sclerosis (PLS)	**2.Epilepsy**	2.**Amyotrophic lateral sclerosis (ALS)**
3.Progressive muscular atrophy (PrMA)	3. **Multiple sclerosis (MS)**	3.Batten's disease (BD)
4.Progressive bulbar palsy (PrBP)	4. **Parkinson's disease (PD)**	4.Creutzfeldt-Jakob disease (CJD)
5.Pseudobulbar palsy (PsBP)	5.Stroke	**5. Dementia**
6.Monomelic amyotrophy (MMA)	**Muscular disorders**	**6. Huntington's disease (HD)**
	1.Muscular dystrophy (MD)	7.**Multiple sclerosis (MS)**
	2.**Amyotrophic lateral sclerosis (ALS)**	**8. Multiple system atrophy (MSA)**
	3.Guillain-Barre syndrome (GBS)	9. **Parkinson's disease (PD)**
	Psychiatric disorders	
	1.Anxiety	
	2.Bipolar disorders (BD)	
	3.Depression	
	4.Schizophrenia	
	Developmental disorders	
	1.Autism-spectrum disorder (ASD)	

	2.Cerebral palsy (CP)	
	3.Spina bifida (SB)	

**Bold faced entries are the subjects of my books, Fymat 2017-2024 – see the References.*

Table 1: Motor neuron, nervous system, and neurodegenerative diseases*

Lambert–Eaton myasthenic syndrome

Lambert–Eaton myasthenic syndrome (LEMS) is a rare autoimmune disorder characterized by muscle weakness of the limbs. It is also known as myasthenic syndrome, Eaton–Lambert syndrome and, when related to cancer, carcinomatous myopathy.

Around 60% of those with LEMS have an underlying malignancy, most commonly small-cell lung cancer (SCLC). It is therefore regarded as a paraneoplastic syndrome (a condition that arises because of cancer elsewhere in the body). It is the result of antibodies against presynaptic voltage-gated calcium channels (VGCC), and likely other nerve terminal proteins, in the neuromuscular junction (the connection between nerves and the muscle they supply). The diagnosis is usually confirmed with EMG and blood tests. It must also be distinguished from myasthenia gravis (a related autoimmune neuromuscular disease) and ALS. The condition affects about 3.4 per million people. It usually occurs in people over 40 years of age but may occur at any age.

Signs and symptoms

The weakness from LEMS typically involves the muscles of the proximal arms and legs. In contrast to myasthenia gravis, the weakness affects the legs more than the arms. Weakness of the bulbar muscles is occasionally encountered. Weakness of the eye muscles is uncommon. In the advanced stages of the disease, weakness of the respiratory muscles may occur. Some may also experience problems with coordination (ataxia). Three-quarters of people with LEMS also have disruption of the autonomous nervous system (ANS) and orthostatic hypotension.

Along with a medical history and physical examination by a neuromuscular physician, a VGCC antibody test and EMG test can obtain a diagnosis of LEMs. However, positive VGCC antibody tests may indicate other diseases.

Causes

While associated with lung cancer (50–70%), LEMS may also be associated with endocrine diseases such as hypothyroidism or diabetes mellitus type 1 or myasthenia gravis.

Mechanism

In normal neuromuscular function, a nerve impulse is carried down the axon from the spinal cord. At the nerve ending in the neuromuscular junction, where the impulse is transferred to the muscle cell, the nerve impulse leads to the opening of voltage-gated calcium channels (VGCC), the influx of calcium ions into the nerve terminal, and the calcium-dependent triggering of synaptic vesicle fusion with plasma membrane. These synaptic vesicles contain acetylcholine, which is released into the synaptic cleft and stimulates the acetylcholine receptors on the muscle. The muscle then contracts.

In LEMS, antibodies against VGCC, particularly the P/O type VGCC and possibly the N-type VGCC antibody, decrease the amount of calcium that can enter the nerve ending, hence less acetylcholine can be released from the neuromuscular junction. Apart from skeletal muscle, the autonomic nervous system also

requires acetylcholine neurotransmission; this explains the occurrence of autonomic symptoms in LEMS. P/Q voltage-gated calcium channels are also found in the cerebellum, explaining why some experience problems with coordination.

Apart from the decreased calcium influx, a disruption of active zone vesicle release sites also occurs, which may also be antibody dependent. Repeated stimuli over a period of about 10 seconds eventually lead to sufficient delivery of calcium, and an increase in muscle contraction to normal levels, which can be demonstrated using needle electromyography.

Diagnosis

The diagnosis is usually made with nerve conduction study (NCS) and EMG, which is one of the standard tests in the investigation of otherwise unexplained muscle weakness. EMG involves the insertion of small needles into the muscles. NCS involves administering small electrical impulses to the nerves, on the surface of the skin, and measuring the electrical response of the muscle in question. Blood tests may be performed to exclude other causes of muscle disease (elevated creatine kinase may indicate a myositis, and abnormal thyroid function tests may indicate thyrotoxic myopathy. Once LEMS is diagnosed, investigations such as a chest CT-scan are usually performed to identify any possible underlying lung tumors. While CT of the lungs is usually adequate, a positron emission tomography (PET) scan of the body may also be performed to search for an occult tumour, particularly of the lung.

Treatment

If LEMS is caused by an underlying cancer, treatment of the cancer could lead to resolution of the symptoms. Firdapse is the only FDA-approved treatment for LEMS. It works in the presynaptic neuromuscular junction to increase the release of acetylcholine helping to improve muscle function and relieve/reduce the symptoms of LEMS.

Immunosuppression

Some evidence supports the use of intravenous immunoglobulin (IVIg). Immune suppression tends to be less effective than in other autoimmune diseases. Prednisolone (a glucocorticoid or steroid) suppresses the immune response, and the steroid-sparing agent Azathioprine may replace it once therapeutic effect has been achieved. IVIg may be used with a degree of effectiveness. Plasma exchange (or plasmapheresis), the removal of plasma proteins such as antibodies and replacement with normal plasma, may provide improvement in acute severe weakness. Plasma exchange is less effective than in other related conditions such as myasthenia gravis, and additional immunosuppressive medication is often needed.

Other treatment modalities

Three other treatment modalities also aim at improving LEMS symptoms, namely Pyridostigmine, 3.4-diaminopyridine *(Amifampridine)*, and *Guanidine*. They work to improve neuromuscular transmission. Intravenous immunoglobulin (IVIg) and *Mestinon* tablets (Pyridostigmine) are secondary treatments.

Multifocal motor neuropathy

Multifocal motor neuropathy (MMN) is a progressively worsening condition where muscles in the extremities gradually weaken. The disorder, a pure motor neuropathy syndrome, is sometimes mistaken for ALS because of the similarity in the clinical picture, especially if muscle fasciculations are present. MMN is thought to be autoimmune. It was first described in the mid-1980s.

Unlike ALS, which affects both upper motor neurons (UMN) and lower motor neurons (LMN) pathways,

MMN involves only the LMN pathway, specifically, the peripheral nerves emanating from the LMNs. Definitive diagnosis is often difficult, and many MMN patients labor for months or years under an ALS diagnosis before finally getting a determination of MMN.

MMN usually involves very little pain; however, muscle cramps, spasms and twitches can cause pain for some people. MMN is not fatal and does not diminish life expectancy. Once undergoing treatment, many patients only experience mild symptoms over prolonged periods, though the condition remains slowly progressive. MMN can however, lead to significant disability, with loss of function in hands affecting the ability to work and perform everyday tasks, and "foot drop" leading to inability to stand and walk. Some patients end up using aids like canes, splints and walkers.

Symptoms

Usually beginning in one or both hands, MMN is characterized by weakness, muscle atrophy, cramping, and often profuse fasciculations. The symptoms are progressive over long periods, often in a stepwise fashion, but unlike ALS, are often treatable. Sensory nerves are usually unaffected. Wrist drop and foot drop (leading to trips and falls) are common symptoms. Other effects can include gradual loss of finger extension, leading to a clawlike appearance. Unlike other neuropathies, cold and hot temperatures exacerbate MMN symptoms to such an extent, that this temperature response is being investigated as a diagnostic tool.

Cause

MMN is thought to be caused by alterations in the immune system, such that certain proteins (antibodies) that would normally protect one from viruses and bacteria begin to attack constituents of peripheral nerves. Antibodies may be directed against "GM-1", a ganglioside found at the Nodes of Ranvier. These antibodies have been detected in at least one-third of MMN patients. More recent studies also suggest that newer tests for antibodies directed against GM-1, as well several related gangliosides, are positive in over 80% of MMN patients. There are increasing reasons to believe these antibodies are the cause of MMN.

Diagnosis

The diagnosis of MMN depends on demonstrating that a patient has a purely motor disorder affecting individual nerves, that there are no UMN signs, that there are no sensory deficits, and that there is evidence of conduction block. These criteria are designed to differentiate the disorder from ALS (purely motor but with UMN signs), the Lewis-Sumner Syndrome (LSS) variant of chronic inflammatory demyelinating polyneuropathy (CIDP) (like MMN but usually with significant sensory loss), and “vasculitis”.

The diagnosis is based on the history and physical examination along with the electrodiagnostic study, which includes NCS and nEMG. The NCS usually demonstrate conduction block. The EMG portion of the test looks for signals in the way muscles fire. Laboratory testing for GM1 antibodies is frequently done and can be very helpful if they are abnormal. However, since only a third of patients with MMN have these antibodies, a negative test does not rule out the disorder. Spinal fluid examination is not usually helpful.

Treatment

MMN is normally treated by receiving intravenous immunoglobulin (IVIg), which can in many cases be highly effective, or immunosuppressive therapy with cyclophosphamide or Rituximab. Steroid treatment (Prednisone) and plasmapheresis are no longer considered to be useful treatments. Prednisone can exacerbate symptoms. IVIg is the primary treatment, with about 80% of patients responding, usually

requiring regular infusions. Other treatments are considered in case of lack of response to IVIg, or sometimes because of the high cost of immunoglobulin. Subcutaneous immunoglobulin is under study as a less invasive, more-convenient alternative to IV delivery.

Spinal muscular atrophy

Spinal muscular atrophy (SMA) is a rare neuromuscular disorder that results in the loss of motor neurons and progressive muscle wasting. It is usually diagnosed in infancy or early childhood and, if left untreated, it is the most common genetic cause of infant death. It may also appear later in life and then have a milder course of the disease. The common feature is progressive weakness of voluntary muscles, with arm, leg and respiratory muscles being affected first. Associated problems may include poor head control, difficulties swallowing, scoliosis, and joint contractures.

SMA is due to an abnormality (mutation) in the SMN1 gene which encodes SMN, a protein necessary for survival of motor neurons. Loss of these neurons in the spinal cord prevents signaling between the brain and the skeletal muscles. Another gene, SMNA, is considered a disease modifying gene, since usually the more the SMN2 copies, the milder is the disease course. The diagnosis of SMA is based on symptoms and confirmed by genetic testing.

Usually, the mutation in the SMN1 gene is inherited from both parents in an autosomal recessive manner, although in around 2% of cases it occurs during early development (de novo). The incidence of spinal muscular atrophy worldwide varies from about 1 in 4,000 births to around 1 in 16,000 births, with 1 in 7,000 and 1 in 10,000 commonly quoted for Europe and the U.S. respectively.

Outcomes in the natural course of the disease vary from death within a few weeks after birth in the most acute cases to normal life expectancy in the protracted SMA forms. The introduction of causative treatments in 2016 has significantly improved the outcomes. Medications that target the genetic cause of the disease include Nusinersen, Risdiplam, and the gene therapy medication Onasemnogene abeparvovec. Supportive care includes physical therapy, occupational therapy, respiratory support, nutritional support, orthopedic interventions, and mobility support.

Signs and symptoms

The symptoms vary depending on the SMA type, the stage of the disease as well as individual factors. Signs and symptoms below are most common in the severe SMA type 0/I:

• Areflexia, particularly in extremities.
• Overall muscle weakness, poor muscle tone, limpness or a tendency to flop.
• Difficulty achieving developmental milestones, difficulty sitting/standing/walking.
• In small children: adopting of a frog-leg position when sitting (hips abducted and knees flexed).
• Loss of strength of the respiratory muscles: weak cough, weak (infants), accumulation of excretions in the lungs or throat, respiratory distress.
• Bell-shaped torso (caused by using only abdominal muscles for respiration) in severe SMA type.
• Fasciculations (twitching) of the tongue.
• Difficulty sucking or swallowing, poor feeding.

Causes

SMA is caused by a genetic mutation in the SMN1 gene. It is mutated in such a way that it is unable to correctly code the SMN protein. However, almost all people have at least one functional copy of the SMN2 gene (with most having 2–4 of them) which still codes 10–20% of the usual level of the SMN protein, allowing some neurons to survive. In the long run, the reduced availability of the SMN protein results in gradual death of motor neuron cells in the anterior horn of the spinal

cord and the brain. Skeletal muscles, which all depend on these motor neurons for neural input, now have decreased innervation (also called denervation), and therefore have decreased input from the central nervous system (CNS). Decreased impulse transmission through the motor neurons leads to decreased contractile activity of the denervated muscle. Consequently, denervated muscles undergo progressive atrophy.

Muscles of lower extremities are usually affected first, followed by muscles of upper extremities, spine and neck and, in more severe cases, pulmonary and mastication muscles. Proximal muscles are usually affected earlier and to a greater degree than distal muscles.

Diagnosis

SMA is diagnosed using genetic testing that detects homozygous deletion of the SMN1 gene in over 95% of cases, and a compound SMN1 mutation in the remaining patients. Symptomatically, SMA can be diagnosed with a degree of certainty only in children with the acute form who manifest a progressive illness with paradoxical breathing, bilateral low muscle tone, and absent tendon reflexes.

Management

The management of SMA varies based upon the severity and type. In the most severe forms (types 0/1), individuals have the greatest muscle weakness requiring prompt intervention. Whereas the least severe form (type 4/adult onset), individuals may not seek certain aspects of care until later decades in life. While types of SMA and individuals among each type may differ, specific aspects of an individual's care can differ.

Medications

Nusinersen (marketed as *Spinraza*) is given directly to the central nervous system using an intrathecal injection. It prolongs survival and improves motor function in infants with SMA. It was approved for use in the U.S. in 2016, and for use in the EU in 2017.

Onasemnogene abeparvovec (marketed as *Zolgensma*) is a gene therapy first approved in the U.S. in May 2019 as an intravenous formulation for children below 24 months of age. Approval in the European Union, Japan and other countries followed, albeit often with different approval scopes.

Risdiplam (marketed as *Evrysdi*) is a medication taken by mouth in liquid form. It is a pyridazine derivative. It aims to increase the amount of SMN protein so that there is enough protein to sustain the peripheral nervous system tissues which are usually the most damaged by SMA. First approved for medical use in the U.S. in 2020, it has since been approved in over 30 countries.

Prognosis

In the absence of pharmacological treatment, people with SMA tend to deteriorate over time. Recently, survival has increased in severe SMA patients with aggressive and proactive supportive respiratory and nutritional support.

If left untreated, most children diagnosed with SMA type 0 and 1 do not reach the age of 4, recurrent respiratory problems being the primary cause of death. With proper care, milder SMA type I cases (which account for approx. 10% of all SMA1 cases) live into adulthood. Long-term survival in SMA type I is not sufficiently evidenced; however, as of 2007 advances in respiratory support seem to have brought down mortality.

In untreated SMA type II, the course of the disease is slower to progress, and life expectancy is less than the healthy population. Death before the age of 20 is frequent, although many people with SMA live to become parents and grandparents. SMA type III has

normal or near-normal life expectancy if standards of care are followed. Type IV, adult-onset SMA usually means only mobility impairment and does not affect life expectancy.

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