

Reaching a diagnosis of MND can take several months since no single test currently exists that will confirm the diagnosis in the way that a blood test, for example, can confirm leukaemia. Your GP may have spent several weeks or months trying to identify the cause of your problems before referring you to a specialist neurology centre.

Many doctors, including some neurologists, do not have sufficient experience with recognising and treating MND. As a result patients are often referred to MND specialist neurologists to confirm a diagnosis.

A Consultant Neurologist will start with an open mind as to the many possible causes of the symptoms displayed by a patient and will gradually eliminate other possible causes by the results of a series of questions and tests. Even then the diagnosis is not definite as one characteristic of MND is "progression," i.e. the condition must be seen to worsen with time. It is the need to observe progression that can delay changing the diagnosis from "Possible MND" to MND.

However, there are clinical signs that can indicate wasting of motor neurons located in the brain (known as "Upper Motor Neurones" or in the neurones that emerge from the spine to carry messages to the muscles, (known as "Lower Motor Neurones.") Doctors familiar with MND usually see some of the following signs of lower and/or upper motor neuron degeneration:

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Lower Motor Neuron Degeneration:

- muscle weakness and atrophy (wasting)
- muscle cramps
- weakened reflexes
- flaccidity (decreased muscle tone)

Upper Motor Neurone Degeneration:

- muscle stiffness, or rigidity
- emotional lability (decreased ability to control laughing or crying)
- increased or hyperactive reflexes

Some of these are signs of normal aging; however, over time, as muscles continue to weaken, and the weakening spreads throughout the body, it becomes more apparent that the cause is MND.

In addition to a physical examination, people are often given an electromyogram (EMG) test, blood tests, an MRI (Magnetic Resonance Imaging) scan and other tests to search for the presence of other diseases that can look like MND.

Common Forms of Onset

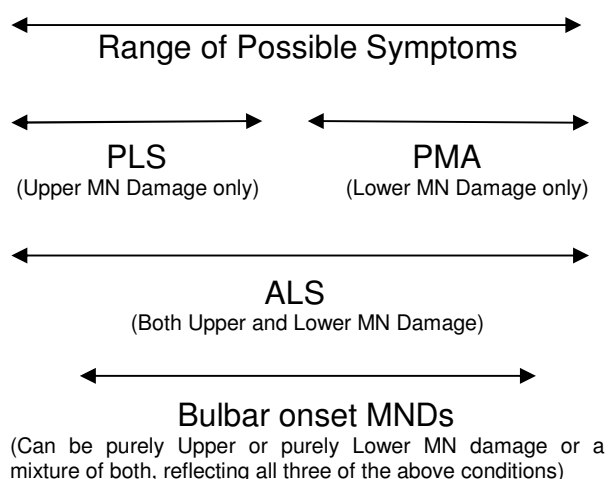
Four common forms of onset of MND can be recognised today, based on the initial symptoms:

- **Primary Lateral Sclerosis (PLS)**, is due to upper motor neurone damage alone,
- **Progressive Muscular Atrophy (PMA)**, is due to lower motor neurone damage alone
- **Amyotrophic Lateral Sclerosis (ALS)**, is due to both upper and lower motor neurone damage

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- **Bulbar Palsy**, the bulbar palsies can be further subdivided into those arising from upper motor neurone damage alone, lower MN damage alone, or damage to both types together. However, some clinicians would strongly argue that their progression makes the bulbar palsies more akin to an aggressive type of ALS that begins with the muscles of the mouth or throat.

The above four forms of MND appear quite separate in their early stages, (as can the bulbar sub-types) but as each of them develops the symptoms can spread to affect other motor-neurones, including those that are involved in the early stages of each of the other forms of MND. Each of these conditions can, therefore, develop overlaps with the other diagnoses that make neurologists question whether they are really conditions different from each other, or one disease with a spectrum of symptoms, some of which are at one end of the spectrum, some at the other end, with no related symptoms, and some sitting in the middle with symptoms linking those at either extreme.



How the symptoms of different MNDs can overlap

An alternative viewpoint is to look at the type of damage sustained by the motor neurones themselves. Examination of motor neurones taken from different patients reveals that there is a number of different causes of death of the motor neurones. In some cases the connections to the muscle become detached and the neurone dies back from that point. In other cases the long connection from the spine to the muscle becomes blocked by broken down parts of the cell skeleton, while in other cases the cell structures that provide the cell with energy become blocked by mutated proteins, so starving the cell to death. There are many other identifiable causes of cell death in MND suggesting that the disease we call MND is actually due to many different mechanisms and therefore many different disease processes, all of which result in the death of motor neurones.

Kennedy's Disease, which is sometimes initially diagnosed as MND, is a form of adult-onset spinal muscular atrophy (SMA), and differs from MND in that it is a chromosomal X-linked recessive disease. This means that there is a mutation to a gene located on the X-chromosome.

Since women have two X-chromosomes the healthy chromosome usually compensates for the damaged one, however, since men have only one X chromosome (and a very small Y chromosome with a different set of genes in place of the other X) there is no second copy of the gene to compensate. Therefore only males are diagnosed with the condition if the Kennedy's disease gene is damaged. It is most often diagnosed between 20-40 years of age, progresses very slowly, and the expected lifespan is often normal. An actual diagnosis of Kennedy's Disease is

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possible through DNA testing. See www.kennedysdisease.org for more information.

Motor Neurone Disease is not, at present, a curable condition. Much research is taking place worldwide into the causes of the condition and possible treatments, but only one drug, Riluzole, is specifically approved in the UK for the treatment of MND. Recent investigations indicate that a combination of Riluzole and another chemical called Lithium Carbonate might be more effective than Riluzole alone and trials commenced in 2009 to investigate this possibility. Riluzole (or Riluzole plus Lithium Carbonate) is not a cure for MND, but does slow the progress of the condition for the majority of patients who take it.

It is through motor neurons that the brain sends messages to the muscles under conscious control throughout the body (muscles whose movement you can control, like your arm and leg muscles, as opposed to those you cannot, like the heart). MND destroys these motor neurons making it impossible for messages from the brain to reach the parts of the muscle where the motor neurones have been lost.

Leg and foot muscles are controlled by lower motor neurons originating in the lower part of the spinal cord. Respiratory muscles (diaphragm and rib muscles) are controlled by lower motor neurons originating in the upper and chest levels (mid section) of the spinal cord while arm, hand and finger muscles are controlled by lower motor neurons coming from the upper spinal cord arising near the neck. In each case an upper motor neurone carries the messages from the brain to the spine and a group of lower motor

neurones carry the messages from the spine out to the muscles.

In the case of muscles located in the neck, throat, face and head the lower motor neurons controlling them arise directly from the brain itself.

MND does not affect the five senses of sight, hearing, taste, smell and touch, nor does it normally affect the eye muscles, heart, bladder, bowel, or sexual muscles.

It is extremely unlikely that MND is infectious or contagious. Scientists have searched for viruses and other organisms that should be found in everyone with MND if it was a disease like the flu or tetanus and have found nothing so far.

At any one time MND affects about six to eight people per 100,000 of population.

With an estimated UK population of 55 million, approximately 4,500 people in the UK currently have MND. In Scotland just now (2009) there are about 130 diagnoses per year and just over 300 people with the condition at any one time. In any given year, about two and a half new cases of MND per 100,000 of population will be diagnosed. The incidence (new cases) of MND within an age group increases with age until about the mid 70s or early 80s. MND most often occurs between the ages of 40 and 70, but it can occur in any decade of life.

As various health initiatives to tackle the most common causes of death become more effective, what had been less common causes of death become more common. We have therefore seen deaths from coronary and circulatory problems decrease in recent years, while those from neurological conditions have increased. In line with this trend and the

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generally aging population it is expected that the number of MND cases will continue to increase in Scotland and the UK for the foreseeable future as the number of over 45s increases.

Although the *average* life expectancy from the first symptoms of MND is between three and five years, 20% live more than five years, and 10% live more than 10 years.

The majority of MNDs appear not to be inherited and are of unknown cause, these cases are therefore referred to as sporadic MND. Between 5% and 10% of cases are of an inherited variety called Familial MND, meaning that the disease has been inherited through a parent. Three different genes have now been identified as being capable of transmitting MND from generation to generation.

Until recently, an abnormally high incidence of MND was observed in the Western Pacific (Guam, Kii Peninsula of Japan and Papua New Guinea).

With the Americanisation of the Western Pacific and reduced dependency on traditional foodstuffs, major declines in the incidence of MND in this region have occurred. As a result it is now thought that these high incidence rates were due to specific toxins that occurred in traditional food sources (for example, a poison contained in flour from palm trees called cycasin). It is therefore possible that unidentified environmental contaminants might be responsible for "triggering" some sporadic cases. Despite the appeal of this idea to explain the late onset of MND and decades of searching, no definite environmental trigger has yet been found.

ALS

Dr. Jean-Martin Charcot, a French pathologist who founded the field of neurology, published the first full account of the symptoms of ALS in 1874. ALS is sometimes known as Charcot's Disease or Lou Gehrig's disease. ALS is the most common form of Motor Neuron Disease (MND) accounting for about 65% of all cases.

What Amyotrophic Lateral Sclerosis means

Most medical "names" are actually a description, often in Greek and sometimes in Latin or other languages of the features that characterise a particular condition. When translated from Greek "Amyotrophic Lateral Sclerosis" breaks down as follows:

A = absence of
myo = muscle
trophic = nourishment
Lateral = side (of spine)
Sclerosis = hardening

i.e. A disease which causes wastage of the muscles and hardening (or scarring) at the sides of the spinal cord.

ALS often begins in one limb before affecting the opposite limb, although cases are known where only one side of the person's body has been affected.

Through time the symptoms of ALS spread from the affected limbs and can affect the other muscles of the body. There is no predictable pattern to this spread. In a small number of cases the disease even appears to stop spreading.

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In about 10% of cases familial ALS can be inherited in what is referred to as a “Mendelian” way. This means that at sometime in the past someone has developed a faulty gene in a sex-cell and this has been passed on so that this mutation is found in all of their descendants who have developed ALS. The damaged gene has “gained a function” due to the mutation and can now cause ALS.

When we pass on our genes like this there is a 50/50 chance of passing on either the good copy or the faulty copy. Not everyone who gets a faulty copy of a gene like this will develop ALS since the same faulty gene may be found in relatives who did not develop ALS before they died. We will never know whether or not they would have developed ALS if they had lived longer. The odds are, if they had escaped all other causes of death, then MND would have caught up with them eventually. Research has shown that about 20% of people who have inherited an ALS gene from a parent do not develop the condition. On the other hand, it is extremely unlikely that descendants who have not inherited the faulty gene will develop ALS at all.

In one recent Scottish case a lady with familial MND reached the age of 92 before developing symptoms of the disease. This is surely evidence that knowing MND “runs in the family” should not unduly influence our life choices as we might only develop the condition if we live long enough. The same is true for the descendants of someone with familial MND who run only a 40% chance of developing the condition. See factsheet 2 “Inherited MND,” for additional information.

SYMPTOMS, SIGNS AND DIAGNOSIS

Symptoms are what you experience, or feel whereas **signs** are what you can see or measure.

The early symptoms of MND may seem vague. They can include tripping unexpectedly, dropping things, slurred or “thick” speech, muscle cramping, weakening, or twitching. Some people with these early symptoms may tend to assume that they are normal signs of aging. Being a progressive disease, MND may spread throughout the body over time. As the disease progresses, the muscles of the trunk of the body can be affected, including weakness of the breathing muscles which can develop slowly over months or years.

MND symptoms, and the order in which they occur, vary from one person to another. The rate of muscle loss can vary significantly from person to person, with some patients having long periods with very slow degeneration.

For some people, the muscles involved in speaking, swallowing or breathing are the first to be affected. These are known as **Bulbar Symptoms**. The term “bulbar” refers to the bulb region of the brain which controls the muscles used for chewing, swallowing, and speaking. There are two common forms of bulbar MND, known as Pseudo-Bulbar Palsy and Progressive Bulbar Palsy.

Primary Lateral Sclerosis (PLS) is different from the other forms of MND in that it does not involve muscle wasting and may progress over decades. In cases of PLS the reflexes remain intact and may become exaggerated (hyper-reflexia.) The expected lifespan may be normal. Damage in PLS is to the upper

motor neurons alone, but reflexes involve only the lower motor neurons and what are called “relay neurons” in the spinal cord. Once control from the brain has been lost the lower motor neuron and relay neuron remain intact allowing reflex actions, but no control from the brain.

Some people diagnosed, initially, with PLS may begin to suffer muscle wastage a few years after diagnosis. This new development causes their diagnosis to be changed from PLS to ALS.

Progressive Muscular Atrophy (PMA) involves only the lower motor neurones. Since there is neither stimulation of the muscles nor reflexes due to lower motor neuron damage they waste away (atrophy).

What causes MND?

Although it has been well over a century since the first complete description of ALS by Dr. Jean-Martin Charcot, there is still no cure or effective treatment and the rate of MND appears to be on the rise. In spite of that painful reality, researchers are making rapid headway in understanding the complexity of the disease and developing future therapies. The accumulation of knowledge about the basic biology and potential mechanisms involved in MND, coupled with impressive technological advancements, is accelerating the rate of progress in MND research. It is commonly believed that more advances have been made in the last ten years than in the last one hundred, and the sense of anticipation in the research community is stronger than ever before. Once thought to be a single disease state, MND is now recognised to have multiple interacting causes, all sharing a common pathway leading to the destruction of the motor neurons.

By understanding the mechanisms that trigger this common pathway, it is hoped we will ultimately understand MND. Through such understanding, desperately needed therapeutic options will be developed. Already, new drug, gene, and stem cell therapies are in development. Due to the complex nature of MND, it is thought that a combination of therapeutic strategies to attack the disease at all levels will ultimately provide the means to alter the course of the disease.

Environmental Factors

Although MND is largely age-dependent, and numbers are on the increase as the average age of the population increases, the rate of increase is greater than would be predicted based on the aging population alone. This suggests to some the role of an environmental factor – an idea supported by several examples in which clusters of MND cases have occurred in a particular geographic area or environmental situation. However, isolating specific environmental culprits has not been possible so far.

Certain lifestyle factors such as diet, alcohol consumption, exercise, and smoking tobacco, as well as environmental factors such as living in rural areas, job related factors, physical injury and pre-existing medical conditions have been studied as risk factors for MND. To date, research findings suggest that only smoking has shown a strong enough positive association to be considered a “probable,” but not yet “established” risk factor.

There is also an increased risk evident in those who have suffered a recent injury, although which is cause and which is effect is arguable. An association with electrical injury has been proposed, but is not proved. More recently, despite

previous investigators drawing a blank when they looked for viruses as a cause of MND, advances in new techniques have caused some investigators to revisit the virus ideas.

Although no single environmental agent has been shown to directly cause MND, worldwide epidemiological studies consistently suggest environmental triggers are important enough to continue to study this possibility to better understand the relationships.

Genetic Factors and Inherited Variants of MND

Approximately 90% of MND cases are described as sporadic and do not show simple inheritance. However, many scientists assume that for many people who develop MND, a genetic predisposition may interact with other factors such as environmental variables to produce the disease.

A wide variety of naturally occurring genetic mutations could produce susceptibility to MND. Recent research suggested genetic defects in dynein, a transporter protein in cells, could provide a common underlying mechanism of ALS and other forms of motor neuron disease.

So far sixteen genetic loci have been implicated in familial forms of ALS, each producing different features of disease in the affected families. Four of these genes have been precisely located and their corresponding protein identified. It has to be stated that not all investigators agree that each of these conditions is a form of ALS, despite them being named as ALS 2, 3, 4 and so on rather than a more generalised motor neurone disease

The best known form of familial ALS is caused by a mutation to the ALS1 gene (also known as the SOD 1 gene) which is found on chromosome 21. The mutation causes the gene to make an abnormal form of the enzyme *copper/zinc superoxide dismutase* (SOD1). Researchers have shown that the chemical made by this mutation has not only a direct effect on the motor neurons, but on their neighbouring support cells as well.

Every newly identified and located MND gene provides scientists with another piece of the MND puzzle and creates the opportunity to develop new animal models and cell lines that simulate and replicate these genetic abnormalities to research the mechanisms that may occur in MND. Even though inherited variants of ALS occur in such a small percentage of ALS patients, these genetic models lend insight into the mechanisms of the disease as a whole.

Genetic testing

Testing for a mutated SOD1 gene is possible, but rarely recommended for a number of reasons. Genetic testing should only be undertaken after formal genetic counselling, which will determine whether or not testing is appropriate for you. Genetic counselling is the process of providing individuals and families with information on the nature, inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. To undertake a genetic test because of an unfounded fear can often have implications for life assurance, building society loans and other forms of insurance, therefore it should not be undertaken lightly. Bear in mind the lady who did not develop MND

until she was in her 90s. How many of us will actually live to be that old?

Currently genetic testing is only able to identify risks associated with known genes. Even though some genes have been identified, the majority of cases of inherited ALS still remain unexplained. There are research projects that seek blood samples from persons with familial ALS to further their work in identifying more genetic loci and better understand the disease process. Ask your neurologist for more information about these studies if you are interested in participating.

Testing might be appropriate for a patient with ALS who has another affected family member or an incomplete family history. Molecular genetic testing could clarify the mode of inheritance (i.e., autosomal dominant, autosomal recessive, or X-linked dominant determined by family history) and modify the risk assessment for genetic counseling as well as perhaps indicating disease prognosis where there are several pre-existing family members who have had the disease.

Presymptomatic testing for SOD1 mutations for adults, who have no symptoms of ALS but do have a family history, is available but controversial because of a condition known to geneticists as “incomplete penetrance.” (Penetrance is a term used in genetics that describes the percentage of people with the genetic mutation who go on to develop the disorder associated with that mutation.)

In MND only about 80% of those known to have genetic mutations which can cause MND actually develop the condition. Inability to predict age of onset

(if at all,) the lack of preventive measures, and the lack of a cure for MND all caution against undertaking a test due to the possible stress that a positive result could cause, even though the gene may never be expressed in some people as they may die of other causes first.

Genetic testing of children

This is often requested by parents and requires sensitive and understanding counselling.

It is generally agreed that children who do not show symptoms should not be tested for adult onset diseases as it removes their choice later in life, increases the chance of social stigmatisation, and could negatively impact on educational, career and other life decisions.

If you are thinking about genetic testing, ask your neurologist about where you can go for genetic counselling and testing. In Scotland there are four Regional Genetics Centres based in Aberdeen, Dundee, Edinburgh and Glasgow. See factsheet 2 “Inherited MND” for contact addresses for these centres.

Is MND Treatable?

Although MND itself is not treatable many of the associated symptoms can be alleviated by prescription drugs. Recommended drugs and doses are listed in our publication “MND A Problem Solving Approach,” which is intended for medical and health care professionals. It is recognised there is a critical need to find treatments to effectively slow the progression of MND, or cure it completely. However, with today's quickly advancing scientific technology, the odds of finding effective treatments for MND are better than ever before.

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Summary

In summary, MND is a complex disorder in terms of how and why motor neurons are destroyed as well as how different individuals are affected. Given this complexity, MND research can be daunting. However, scientists continue to make progress in better understanding

the disease pathways. Likewise clinical researchers continue to conduct trials to gain more insight into effective therapies. With scientific technology moving ahead at a very rapid pace, there is more hope than ever in the fight against MND. See factsheet 47, 'Recommended Reading' for lists of books, videos, and websites about MND.

Further Information

Factsheet 2	Inherited MND
Factsheet 3	Introducing Human Inheritance
Factsheet 16	Stem Cells
Factsheet 18	Understanding Clinical Trials
Factsheet 47	Recommended Reading

"MND, A Problem Solving Approach for general practitioners and health and social care professionals" is available on request to health and social care professionals.