

# Motor Neurone Disease

## What is motor neurone disease?

Motor neurone disease (MND) is a fatal and progressive neurodegenerative disease that attacks specialised nerve cells in the spinal cord and the brain, called motor neurones, which control the voluntary movement of muscles. MND is also known as Lou Gehrig's disease, *maladie de Charcot* and amyotrophic lateral sclerosis.

Lou Gehrig was an American baseball celebrity who died of the disease. Dr. Jean-Martin Charcot, a French neurologist, first described MND in 1869. He was the first to link symptoms of the disease to a group of nerves specifically affected – the motor neurones that originate in the spinal cord. "Amyotrophic" refers to the loss of muscle mass; "lateral" refers to the nerve tracks that run down both sides of the spinal cord, where many of the neurones affected by MND are found; "sclerosis" refers to the scar tissue that remains after damage to the nerves has occurred.

Motor neurones reach from the brain to the spinal cord and from the spinal cord to the muscles throughout the body. When motor neurones die, the ability of the brain to initiate and control muscle movement is lost. Patients are often initially prompted to seek medical advice because of a persistent muscle twitch, muscle fatigue, or even muscle wasting.

This usually starts in the hands or lower legs, often accompanied by cramps. As MND progresses, patients lose the ability to dress and feed themselves, sit up, walk, or even speak. The bodily functions that remain intact until or near death are the control of urination and bowel movements, sexual function, eye movement, and intellect. Generally, patients survive three to five years after diagnosis. Death usually occurs due to respiratory failure.

**MND is a progressive disease of the nerves in the spinal cord and brain. As it progresses it leaves patients unable to move but mentally alert. Research is continuing to discover the cause and to find medicines that can improve the lives of patients with this devastating disease.**



### **Who does motor neurone disease affect?**

Although it can affect anyone, MND is most prevalent in the age range of 40 to 70 years and about 20 per cent more common in men than in women. The cause of the disease is still unclear. About 10 per cent of MND cases are inherited. Of those, 20 per cent are caused by mutations in a gene on chromosome 21 called SOD1 (super oxide dismutase 1). Over 60 mutations or structural defects of the SOD enzyme have been found which alter the enzyme's ability to protect against damage to motor neurones.

About 90 per cent of all cases in the general population are undetermined and have no known cause. MND occurs throughout the world, with no racial, ethnic or socioeconomic boundaries. With an incidence of two per 100,000 people, it is estimated that about 10,000 cases are diagnosed in Europe each year. As many as 50,000 Europeans have the disease at any given time.

### **Present treatments:**

Present treatment of MND is aimed at symptomatic relief, prevention of complications and maintenance of optimal function and optimal quality of life. Most of this is targeted at the later stages, and requires nursing management of a patient who is alert but functionally quadriplegic with intact sensory function, bedridden and aware he or she is going to die.

The first treatment to alter the course of MND has been available since 1995. This antiglutamatergic medicine appears to prolong the life of people with MND and more recent studies suggest that the compound also slows the progress of the disease, allowing patients more time in the higher functioning states. Recently, a catalytic antioxidant compound which destroys oxygen-derived free radicals has received orphan drug status to treat patients with MND.

### **What's in the development pipeline?**

There are findings that transgenic mice with MND live longer when treated with a tetracycline antibiotic or the dietary supplement creatine. Researchers have shown that the antibiotic stops "cell suicide" (neuronal apoptosis). Apoptosis includes the activation of nitric oxide and caspase enzyme. Both processes are believed to be involved in the pathology of MND. Other scientists have demonstrated that the antibiotic has a better effect when combined with a calcium channel blocker and an anti-glutamate medicine.

Therefore, research into different combination therapies is underway to explore their effectiveness in patients with MND. An inhibitor of neuronal GAPDH-dependent programmed cell death is also under investigation in clinical trials. Furthermore, clinical studies with an anti-oestrogen medicine and a COX-2 inhibitor have been started.

### **The longer-term future**

It has been shown that insertion of the gene for glial-derived neurotrophic factor, or GDNF, slows the progression of MND in mice. The same holds for the genes that encode for the glutamate transport protein. Inserting extra genes for the protein may be an approach to cleaning up the chemical glutamate which acts on the nervous system from the area around nerve cells. Excess glutamate is thought to be a factor in MND.

Additionally, laboratory research has revealed that genetic flaws in a cell supply line cause a human disease similar to MND. The findings suggest that blockade of the supply line that is required for transporting nutrients and growth factors within nerve cells could be a pivotal event leading to the disease. Motor neurones are distinct from other neurones in the body because of the remarkable lengths of their extensions or axons, which can extend up to a metre.

Thus motor neurons are especially dependent on active axonal transport from the cell body to the neuromuscular junction and vice versa. Researchers have found that outward transport requires motor proteins known as kinesins, while inward transport is based on the motor protein dynein and its activator dynactin. Molecular deviations of these proteins may open new avenues to understand and treat MND in the future. All these findings have yielded important knowledge on the cell death mechanisms of motor neurones in MND.

In 2008, a study group published results which show that the TDP-43 protein is directly toxic to motor neurones and causes degeneration of these cells. TDP-43 is a major component of the pathological hallmarks that are found in MND. It is a predominantly nuclear protein involved in the regulation of messenger RNA transcription and splicing.

Apparently, the TDP-43 protein targets motor neurons, instead of being an innocent by-product of the disease process, as was previously thought. The researchers found that mutations in a gene coding for the TDP-43 protein caused MND in one particular family affected by the rare, inherited form of the disease. This result follows recent research linking the accumulation of TDP-43 protein in nerve cells of people with MND but not in unaffected individuals. This new information is an avenue to greater understanding of the processes that cause motor neurons to die.



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Design & Production - Megaluna

Last update: July 2009