What we know, don't know and suspect about what causes motor neuron disease

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Some types of MND start with a loss of grip. But what causes this? Credit: www.shutterstock.com.au

Since 2014, the ice bucket challenge, which involves people pouring a bucket of icy water over their heads, has raised awareness and much-needed research funds for motor neuron disease. While research for a cure is underway, first we need to know what causes it.

MND affects two per every 100,000, or approximately 420,000 people

worldwide. It occurs in all countries of the world, and does not discriminate based on race, ethnicity or socioeconomic status.

MND is the name given to a group of diseases in which the motor neurons that control muscles progressively die. Motor neurons are cells in the brain and spinal cord that allow us to move, speak, swallow and breathe by sending commands from the brain to the muscles that carry out these functions.

Motor neurons can be divided into either upper motor neurons, which live in the main brain region and project into the brainstem and spinal cord, or lower motor neurons, which reside in the brainstem or spinal cord and directly innervate muscles.

Normally, upper motor neurons transmit signals to lower motor neurons, directing them to make movements. The lower neurons then signal the muscles themselves, controlling normal movements. When the signal is disrupted at some point in the pathway, it affects the ability of muscles to contract and move.

MND is classified, in part, by whether the upper or lower neurons are the ones degenerating and dying. In amyotrophic lateral sclerosis (ALS) or Lou Gehrig's disease, the most common type of MND, both upper and lower motor neurons are affected. Other types of MND may just affect one or the other, and each condition has slightly different symptoms.

Disease of the upper motor neurons causes stiffness of muscles (spasticity), muscle weakness and exaggerated tendon reflexes, such as knee jerks. But if the lower are primarily affected, muscles no longer receive innervation, causing them to weaken and waste away (atrophy), while also developing uncontrollable twitches (fasciculations) and losing their reflex responses.

If both are affected, symptoms usually start mildly with a loss of grip, a slurred word or stumbling while walking. The disease then spreads as motor neurons continue to die, affecting all skeletal muscles, which are under control by the central nervous system. This leads to muscle weakness and atrophy on both sides of the body.

Muscles become spastic, spasm and display uncontrollable twitches. In 75% of individuals, muscles of the face and throat that control speech, swallowing and chewing also become weak and waste away, leading to slurred or nasal speech and difficulty eating. Over time, the disease spreads to muscles of the diaphragm and chest, leading to an inability to breathe without mechanical support, and eventually, death.

Symptoms of MND can vary from person to person, and the rate of progression can also differ widely between individuals. However, it does progress in all cases. For the majority of people, this period of disease progression is quite rapid, with most living two to five years after the onset of symptoms. Only 20% of patients live for five years, 10% for ten years and 5% for 20 years or more. One famous notable exception is the theoretical physicist Stephen Hawking, who was first diagnosed at age 21 and is now 75 years old, meaning he has lived with the condition for over 50 years.

The cause of most cases of MND is currently unknown, although multiple hypotheses have been put forward. This is currently an area of major research throughout the world.

Genetic causes

A small number of cases of MND (5-10%) are inherited from family and can be attributed to a specific genetic mutation, or an alteration in the sequence of DNA. It's estimated that, currently, about 60% of the genes associated with familial MND have been identified. For most

MND genes, an individual only needs to inherit one copy of the mutated gene to cause the disease.

The first gene mutation to be discovered in MND was one called "SOD1", in 1993. SOD1 mutations account for about 10-20% of cases of familial MND (and 1-2% of sporadic cases). While it's unclear exactly how changes in this gene lead to MND, it's thought that it takes on a toxic property, leading to damage in the brain cells and, eventually, death of motor neurons.

Another important gene implicated in familial MND is "C9orf72", which was found in 2011 and is known to be the most common genetic cause of MND. Mutations in this gene account for 25-40% of familial MND (and 7% of sporadic cases). This gene has also been shown to account for 25% of cases of another neurodegenerative disease, a type of dementia called frontotemporal dementia.

This gene contains abnormal repetitions in the DNA code, called repeat expansions. While healthy individuals have up to 30 of these repetitions, individuals with MND, frontotemporal dementia or both can have hundreds or even thousands of repeats. But it's still a matter of debate how this could lead to the development of the disease, with several potential mechanisms put forward, and further research needed.

In addition to these two major genetic discoveries, several other genes have been implicated (NEK1, TDP43, FUS and UBQLN2) that appear to play a smaller role in the number of cases of MND they cause.

It's important to remember, though, that genetic mutations play a small role in most cases of MND. While 5-10% of cases are familial, with a clear genetic link, the other 90-95% of cases are sporadic and are likely to be due to a complex interaction of genetic risk factors and environmental variables.

Age and gender

Non-genetic factors that may contribute to the development of MND have been extensively studied over the years, with several potential causes emerging. One of the major risk factors for MND is advancing age. MND is rare before the age of 40, with an average age of onset of 58-63 years for sporadic MND and 40-60 years for familial MND.

The ice bucket challenge went viral all over the world, spreading awareness of MND. Credit: NBA Yao school/AAP

Males are also more likely than females to have MND, but we don't know why.

Lifestyle causes

A number of lifestyle risk factors for MND have also emerged. Smoking is known to increase the risk of MND, with one study indicating smokers were 42% more likely to be diagnosed with MND, while former smokers had a 44% higher risk.

Certain dietary factors, such as higher intake of antioxidants and vitamin E, have been shown, at least in some studies, to decrease the risk of MND.

Interestingly, increased physical fitness and lower body mass index (BMI) have been shown to be associated with a higher risk of MND. The diagnosis of baseballer Lou Gehrig led scientists to theorise that strenuous physical activity and excessive use of muscles could contribute to the development of MND.

While evidence for this has been inconsistent, an increased risk for MND has been demonstrated among professional soccer players, and MND patients have higher levels of vigorous physical activity compared to individuals without MND. Other factors, however, may account for this relationship, such as repeated head injuries, another purported cause of MND.

A number of occupations have also been found to be associated with increased risk of MND, including electrical workers, farmers, house painters and military personnel. Other individuals exposed to electromagnetic fields, certain chemicals, pesticides and heavy metals, such as lead, manganese, iron and selenium, during the course of their work are also at risk.

But it's still unclear how exposure to these toxins may lead to the development of MND, and not all studies in this area have been

consistent in demonstrating increased risk. Another issue with these toxin exposure studies is that many rely on self-reports, with individuals having to recall their past exposures. This can lead to recall bias, where people with the disease are more likely to report a past exposure, leading to an over-inflation of risk.

Other illnesses

Exposure to viruses has also been cited as a potential cause of MND. Polio virus, for example, can infect motor neurons, and may be linked to later weakening of these neurons.

Retroviruses, such as HIV, have also been shown to be potentially linked to the development of MND.

In addition to viruses, other medical conditions may also be linked to an increased risk of MND. Type I diabetes has been shown to be associated with a threefold increase in risk (although, interestingly, Type II diabetes was associated with a lower risk for MND).

Consistent with other neurodegenerative diseases, such as Alzheimer's and Parkinson's disease, increased inflammation has also recently gained attention as a potential cause of MND. One study showed that, in MND, inflammatory cells called macrophages can ingest motor neurons.

What makes treatment so complicated?

Despite decades of research, there is only one treatment currently approved for MND, a drug called riluzole (Rilutek), first approved by the US Food and Drug Administration in 1995. This aims to reduce the release of the neurotransmitter glutamate from motor neurons, which was once thought to drive the death of these neurons. But the drug doesn't reverse nerve damage or muscle weakness caused by the disease,

and only prolongs life for about three months.

Aside from riluzole, most current treatments such as muscle relaxants or physical therapy attempt to maintain patient quality of life.

In May 2017, the US approved the first new treatment for MND in 22 years, a drug called Radicava (edaravone), which is expected to be on the US market by August 2017. This drug, originally developed for the treatment of stroke in Japan, was approved in 2015 for the treatment of MND in Japan and South Korea.

The drug aims to prevent damage of neurons, and the company that developed it reports it can slow the physical decline of MND patients by 33%.

The drug, which is not a cure and only slows disease progression, is stunningly expensive, costing nearly US$150,000 a year. And patients in the last stage of the clinical trial that led to approval in the US were only followed up to six months, so the long-term benefits of the drug are unknown. The drug is not yet approved for use in Australia.

The causes of MND are many and complex. This is further complicated by the fact we don't know what ultimately causes the death of motor neurons when someone has MND. If we could find this out, then we may well be on the way to developing more effective, and perhaps even curative, therapies for the disease.

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