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In Australia, one in every 15,000 people are affected by motor neurone disease. However, the cause of most cases of MND is unknown; only approximately 10% of all cases are inherited with certainty.

Several specific genes, such as TDP-43, FUS and SOD1, have now been firmly linked to the inherited disease; even so, a proportion of inherited or 'familial' cases of MND are still not linked to a particular gene. Although research has not identified clear causative agents for the remaining approximately 90% of sporadic MND, the scientific community are beginning to unravel some of the molecular events that occur during MND.

Of particular interest is research that has shown that in MND patients motor neurones are not lost gradually over one's lifetime, but are lost in a sudden cascade of events. Therefore, it is likely that environmental factors play a role in triggering disease onset. This is consistent with increased incidences of MND among various populations such as in Gulf War Veterans and professional football (soccer) players in Italy. Generally speaking though, although MND affects slightly more males than females, there is no difference in prevalence based on ethnicity or other demographic variable apart from age.

Recently, there have been a number of studies examining the epidemiology of MND. In this report we will look at these and some of the other MND research going on all around the world.

What is epidemiology?

The word epidemiology originates from the Greek words *epi*, *demos* and *logos*, meaning among, people and study. This translates to the study of what is among or happening to people.

Epidemiological studies are designed to reveal relationships between disease and exposure of people to things such as alcohol or smoking, biological agents, chemicals, or other kind of stress. Therefore epidemiology is the study of the distribution of disease frequency in human populations.

When studying the distribution of the disease one must consider such questions as "who is getting disease within a population", and "where and when is the disease occurring". This knowledge will not only describe patterns of disease but will uncover possible causal relationships or preventive factors.

Head trauma associated with development of motor neurone disease

It has long been suspected that complex interactions between genetic and environmental risk factors bring about MND. Most commonly, a history of trauma to the brain and/or spinal cord, and strenuous physical activity have been thought of as possible triggers of MND onset. Only last month, researchers in Greece have even suggested that cocaine abuse can trigger the development of young-onset MND.

Coincidentally, repetitive head injury is associated with the development of a condition known as chronic traumatic encephalopathy (CTE). Researchers from Boston examined cases of CTE and found an association with TDP-43 accumulation (also known to be associated with MND). Of interest was the fact that three athletes with CTE also developed a progressive motor neurone disease. This link between TDP-43 and the patients that went on to develop a motor neurone disease is the first pathological evidence that repetitive head injury experienced in contact sports might be associated with the development of a motor neurone disease.



Oxygen deprivation a risk factor for MND?

Continuing on with the theme of strenuous physical activity and MND, a research group in Rome, Italy wondered if a person's place of employment was related to MND. Recently, researchers from Michigan, USA have suggested that exposure to metals such as lead or mercury was not by itself a risk factor for MND. However, it has been hypothesised that deprivation of oxygen may be associated with MND. It is known that fluctuations in oxygen levels in blood or tissues is normal. For example, during strenuous physical exercise, blood oxygen levels are decreased, but can lead to a state in which the body is deprived of adequate oxygen supply. This is known as hypoxia. The researchers studied almost 15,000 cases of MND and almost 60,000 deceased from other selected causes of death. The risk associated with physical activity and occupations leading to intermittent hypoxia, such as fire fighters and professional athletes, were analysed. The researchers found that in the population studied, physical activity in general did not increase risk of MND. However, risk associated with occupation as a professional athlete was elevated and fire fighters showed a significant two-fold increase in MND risk. The authors conclude that occupations that are exposed to environments which produce oxygen deprivation or hypoxia might be a risk factor for MND.

Motor neurones unplugged

The distance between the brain and the muscles they innervate is large enough to fit hundreds of thousands of cells side by side. However, the best way to get the signal from the brain to the muscle is to have one cell take the message a really long distance. Motor neurones take this message from the brain to the spinal cord (upper motor neurones), at which time they pass the signal to another motor neurone that takes the message to the muscle (lower motor neurones). The connection between neurones is called a synapse, and acts just like an extension lead plug. There has been ongoing debate as to whether the upper or lower motor neurones are the root of dysfunction in MND. Regardless, the end result is that the signal to the muscles is unplugged and as a result movement cannot occur. Researchers from Rome, Italy have found that there are signs that the connection or synapse between upper and lower motor neurones is faulty. They provide evidence that there is a problem with the upper motor neurones passing the signal on. The authors also demonstrate that these events take place before the appearance of motor symptoms. The next step would be to find a way to "plug back in" to restart the signal flow.



type 2, affects TDP-43 toxicity in animal and cellular models. To assess the involvement of ataxin-2 in MND, the researchers analysed the gene sequence of the ataxin-2 gene in 915 MND patients. The results showed that variations in ataxin-2 were significantly associated with MND. These results establish ataxin-2 as a gene that makes people susceptible to MND. The researchers also add that the findings indicate that the interaction between TDP-43 and ataxin-2 may be a promising target for therapeutic strategy in MND.

New garbage man inside neurones?

It is well known that protein junk piles accumulate inside motor neurones in people with MND. A research group working in Italy has studied a protein called HspB8, found inside neurones, and discovered that it can help in cleaning up the mess. Its job seems to be to recognise these protein junk piles and recruit a degradation system similar to a garbage disposal. The researchers suggest if they can find a way to create more of this HspB8 protein inside neurones it could potentially be used to reduce the protein junk piles in MND patients.



Evidence for interactions between TDP43 and FUS

It was recently found that mutations in two related proteins, TDP-43 and FUS/TLS cause familial MND in a small number of families. It has been proposed that these two proteins perform similar functions, although this has not been proven. Researchers from Wisconsin, USA have recently shown that TDP-43 and FUS directly interact in cells. The significance of this TDP-43-FUS/TLS interaction was established by showing that removing either the TDP-43 or FUS gene resulted in downstream effects such as lowering the concentration of messenger molecules (messenger RNA). Messenger RNA is a "template" of the DNA that encodes a particular gene which is used to build a string of amino acids called a polypeptide or protein. Both TDP-43 and FUS/TLS associated directly with messenger RNA in the test tube. The findings imply that TDP-43 and FUS not only perform a similar role in the cell but actually interact with one another. This has implications for understanding what may be happening during neurone death in MND.

Two wrongs don't make a right

The relationship between TDP-43 and MND are poorly understood, although TDP-43 has been suggested to have a critical role in disease pathogenesis. Researchers from Philadelphia, USA have shown that ataxin 2, a protein mutated in spinocerebellar ataxia

MND Research Shorts

- Researchers in Canada have found that a drug called Calpastatin can suppress mutant SOD1 toxicity to neurones grown in the laboratory. This may be a promising lead for future testing in mice and then, if successful, humans.
- Scientists in Chicago, USA have created an internet browser that can be controlled by the brain alone. The MND patients that trialled the computer:brain interface achieved 72% accuracy using the browser.
- Researchers in Baltimore, USA have come across a drug, Olesoxime, which they think may have some benefits for MND patients. So far it has shown promise in protecting neurones in test tubes and in MND mouse models. They have completed phase I trials, which means the drug is well tolerated in humans. Phase II trials, to test how well the drug works, are in progress in Europe.
- Researchers in Massachusetts, USA have taken creatine into clinical trials. It appears that creatine can cross the blood-brain barrier, is increased in the brain and seems to decrease the concentration of the neurotransmitter glutamate. Reducing glutamate is important since it is thought to be toxic to motor neurones in MND patients.