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Despite the continuing and growing efforts of researchers around the world an effective treatment for motor neurone disease still eludes us. This problem is currently compounded by the lengthy diagnostic process associated with MND. This means by the time a diagnosis is conclusive, a patient may have already lost many of their motor neurones. Lost motor neurones cannot be regenerated, so the earlier we can stop the disease the better the outcome will be. Therefore, discovering ways to diagnose MND earlier is just as important as discovering drugs that slow or arrest disease progression. For this reason, diagnostic MND *biomarkers* must be uncovered and validated to maximise the effectiveness of future treatments. In addition, biomarkers could find other important uses. One possible reason that drug therapies have not been successfully translated from MND mice to humans is that not all cases of MND progress in the same way. Discovery of *biomarkers* that can monitor MND progression would aid the design and implementation of human clinical trials and may even provide novel targets for future therapeutic strategies.

A number of studies detailing possible MND *biomarkers* have been published in the last three months. In this report we will look at these studies and some of the other MND research going on all around the world.

MND biomarker search

It is becoming clear that a precise measure of MND disease progression is urgently required. Many research groups around the world have joined the search for the optimal biomarker. One of the simplest types of molecule to use as biomarkers are proteins. These can easily be measured in a patient's blood or spinal fluid. This has meant that many researchers are sampling MND patients' spinal fluid for proteins that change in concert with MND progression. An obvious place to start would be genes associated with familial MND. This is just what Professor Marklund in Sweden has done by examining the presence of mutant SOD1 in spinal fluid of familial MND patients. The researchers found that although they can detect SOD1 in spinal fluid it would not be a suitable biomarker. On the other hand, work coming out of Chiba in Japan showed that the product of the MND associated gene TDP-43 could be found increased in spinal cord fluid of MND patients. This was specific to MND and changed depending on the stage of the disease. These results mean that TDP-43 shows promise as a biomarker.



Other protein biomarkers are also showing promise. Researchers at the University of Pittsburg, USA have shown that cystatin C has potential as an MND biomarker, while researchers in Sergipe, Brazil have found that the presence of the neurofilament heavy chain in spinal fluid may also be a good predictor of MND. While protein levels in blood plasma and spinal fluid are easily detected and monitored, there may be less invasive ways to monitor MND progression. One such method has been published by Professor Matthew Keirnan's research group in Sydney. They have found that performing functional assessment and nerve conduction studies gives reliable information about MND progression. In addition, a group in the USA has shown that magnetic resonance spectroscopy may be useful as a biomarker. These studies may become very useful for the implementation of clinical trials.

What is a biomarker?

A biomarker, or biological marker, is a substance used as an indicator of a biological state. It is a characteristic that can be objectively measured and evaluated as an indicator of specific processes.

A biomarker can indicate a change that correlates with the risk or progression of a disease. Biomarkers can usually be detected and measured in parts of the body like the blood or other tissue. They may indicate either normal or diseased processes in the body.

For example, body temperature is a well-known biomarker for fever. Cholesterol values are a biomarker and also a risk indicator for coronary and vascular disease. It is also well known that blood sugar levels are a biomarker for diabetes.

MND Research Shorts

- While most people use yeast to make bread or beer, researchers have been busy in Chicago, USA using yeast to fight MND. They have found that the MND gene FUS behaves similarly in yeast as it does in motor neurones. They propose that yeast may be a good model for studying MND.
- One of the largest genetic risk factors for Alzheimer's disease is the e4 version of a gene called ApoE. Researchers in France have tried to link this gene to MND. They found that the e4 ApoE gene was increased in bulbar onset MND, but only in men. The actual contribution of this gene to MND is unknown.
- Researchers from France have also examined genes that control iron metabolism and their possible association to MND. They found that there was a significant association with a gene called SLC11A2. The researchers propose that this implicates iron metabolism in MND and means SLC11A2 could potentially modulate MND progression.

New gene signals problems with protein disposal inside motor neurones?

In another breakthrough study, researchers from the ITALSGEN consortium, Italy and the NIH, USA led by Dr Bryan Traynor have identified a mutation that causes MND in the valosin-containing protein gene (VCP) in an Italian family. VCP is not similar in function to the recently discovered TDP-43 and FUS genes which are implicated in messenger RNA processing. Instead VCP has a protein disposal function. Each and every cell in your body is built from a range of molecules, the majority of which are proteins. As time goes by, these get old and need to be replaced. In order to have space to fit the replacement proteins it is important to dispose of the old ones. 'Micro machines' inside the cells take in



whole proteins and break them down to small pieces, in a similar way to a mulcher taking in tree branches and making them into mulch. This new discovery links this 'mulching' or protein disposal process to MND. So although more research needs to be performed, it may mean that faulty protein disposal leads to MND. Researchers in London, UK have linked this process to another of the familial MND genes. The mutant vesicle-associated membrane protein gene (VAPB) is responsible for cases of familial MND and appears to be resistant to the kind of protein disposal VCP is involved in. The VAPB mutant acts like a stubborn branch that clogs the mulcher. This kind of blocking ability has previously been reported for SOD1, possibly linking some of the various genetic causes of MND. With this in mind researchers at Kumamoto University in Japan have shown that increasing the protein called Derlin-1 lowers the levels of SOD1 in the cell by aiding the cells' disposal process. Derlin-1 may be one way the power of the micro mulchers could be harnessed to treat MND.

Needle in a haystack?

A hallmark feature of MND pathology is tiny junk piles called inclusions. These tiny structures could be likened to haystacks in that they are a 'lump' of smaller elements piled high in a random fashion. It is likely that these stacks are not made from one element, but more probably consist of a number of main elements. Researchers in Japan have shown that some of the 'pieces of hay' are actually made up of a protein called peripherin. The gene that makes peripherin is also known to be a risk factor of MND. So if we find out what these 'haystacks' are made from we may well discover more MND genes.



Mercury not responsible for MND?

Roger Pamphlett's group in Sydney, Australia has tested the hypothesis that mercury poisoning could play a role in MND pathology. The researchers examined the brains and spinal cords of mice exposed to mercury and could not find any evidence that mercury induced the characteristic pathology seen in MND patients. The researchers conclude that their data does not support the hypothesis that mercury may induce MND pathology.

Clinical trial news

Researchers in Tennessee, USA have tested the drug used for some of the congenital myasthenic syndromes in a small number of MND patients. The drug, 3,4-diaminopyridine or DAP, is a potassium channel blocker. This allows more calcium to enter the muscle thus increasing the signal to the muscle.

The researchers were hoping to see a reduction in muscle fatigue in MND patients. Some of the patients had side effects such as tingling lips and fingers, but the researchers report that overall there were modest improvements in muscle fatigue and weakness over the four-week study. So although this drug may not extend patient survival it appears safely tolerated and may show some symptomatic benefit. Larger studies will have to be performed to confirm this.

In a similar study, researchers have taken riluzole, the only drug shown to have benefit in MND patients, and are testing this on another disease of motor neurones; spinal muscular atrophy (SMA). This seems to be tolerated and further studies will have to be conducted to test its usefulness.



A study completed by the STEMALS study group in Italy has shown that the drug Granulocyte Colony-Stimulating Factor (G-CSF) is showing promise as a potential MND treatment. It is well established that MND is associated with a process of inflammation in the brain and spinal cord. This treatment aims to reduce this inflammation and stop further unwanted damage to neurones.

The results showed that indicators of inflammation associated with MND, such as a marker known as MCP-1, was reduced upon treatment. The researchers measured only small decreases in motor function during the study.

Further testing will need to be performed to see how the drug performs in the long term.