mnda
motor neurone disease association

Research

Biomarkers

Information Sheet G

The purpose of this information sheet is to explain what biomarkers are and why they are useful for diagnosis and treatment of a disease, and motor neurone disease (MND) in particular. It also includes examples of some of the currently used biomarkers in MND research.

The content is split into the following sections:

Disclaimer: *Please note that information provided in this information sheet is based on a review of the currently available literature. This information sheet was written by MND Association staff who are not clinicians, so any information provided in this sheet should not be considered clinical advice. You should always discuss potential treatments with your clinician.*

This symbol is used to highlight **our other publications**. To find out how to access these, see *Further information* at the end of this sheet.

What do the words and abbreviations mean?

ALS Functional Rating Scale (ALSFRS):	A rating scale used by doctors to assess progression and severity of MND.
Biomarker:	Unique biological signature of a specific disease, or group of diseases.
Cerebrospinal fluid (CSF):	Cushioning fluid encasing the brain and spinal cord.
Electromyography (EMG):	Procedure for detecting muscle fasciculations.
Magnetic Resonance Imaging (MRI):	A type of scan that creates detailed images of the organs and tissues of the body.
Neurofilaments:	Proteins that make up the skeleton of a neurone.
Ribonucleotic acid (RNA):	Cell's copy of our genetic information (the DNA), important in the process of making new proteins.

1: What is a biomarker?

A biomarker, or 'biological marker', is an observable biological measure that confirms presence of a disease and how far it has progressed. Generally, biomarkers can range anywhere from simple calculations of the body mass index (BMI) to detect malnutrition or obesity, to more detailed analyses of cells in various body tissues (e.g., excess of specific chemicals in the blood or changes in brain structure).

Knowing biomarkers of a specific disease can help clinicians to diagnose a patient faster and more efficiently by simply looking at their biomarker values. Observing changes in these biomarkers can also help track the disease and monitor if it progresses to further stages. By tracking the disease in this way, monitoring biomarkers is an important part of designing clinical trials. As a consequence, biomarkers can potentially lead us to a more efficient treatment as drugs could be provided at the very early stages of the disease, possibly increasing their beneficial effects.

2: Biomarkers in MND

At the moment, diagnosis of MND is usually given after the symptoms have been present for a substantial amount of time. Obtaining such a diagnosis is a lengthy process as there is no simple test that would either confirm or rule out the presence of MND. Instead, a person is diagnosed with MND by excluding other neurological disorders. Knowing specific biomarkers that would act as a 'unique fingerprint' of the disease would allow researchers and clinicians to develop a simple test that would identify MND exclusively.

So far, progression of MND is tracked by looking at the patient's score on the ALS Functional Rating Scale (ALSFRS), an established measure used by clinicians and researchers. Together with survival, this scale is often used in clinical trials to see whether a tested drug is working or not.

However, as MND is associated with alterations in the brain and certain chemicals in the body, researchers are attempting to find a biomarker that would track these changes more directly. Below, we describe the types of biomarkers that are currently the focus of investigation. It is important to note however that all biomarkers are still being researched for their effectiveness and reliability and **there is not yet an established biomarker for MND**.

Below we provide a short summary of a selection of biomarkers that are currently used in research while still being developed to increase their reliability. These biomarkers can be categorised into three groups: neurochemical biomarkers, neuroimaging biomarkers and muscle measurements.

Neurochemical biomarkers

One way to identify MND biomarkers is to look at specific molecules that are present in abnormal levels in people with MND. These can be observed in the blood, urine or cerebrospinal fluid (CSF). Below are a few examples of neurochemical biomarkers that are either currently being used in clinical studies or that are still under investigation.

Neurofilaments
One of the commonly-used biomarkers in clinical studies are neurofilaments – rod-like proteins that make up the skeleton of a neurone. In MND, when motor neurones become damaged, the internal skeleton collapses, inevitably leading to death of the neurone. As the cellular membrane (i.e., coating of a cell) is also disrupted, the contents of the cell (including neurofilaments) are released into the motor neurone's surroundings.

From here, neurofilaments can travel to the blood and CSF, where their presence can be detected by complex biochemical analyses. As the number of degenerated motor neurones increases (which coincides with the progression of MND), the count of neurofilaments in the blood and CSF is higher. Monitoring the levels of neurofilaments over time could therefore help us estimate the stage of disease progression.

p75
Another approach to tracking MND is to look for proteins associated with neurological injuries in urine. One such protein, p75, is normally only detectable during the development of our nervous system in the embryonic stage or when there is damage to the neurones. When a neurone is injured, the p75 'sheds' from the membrane of the neuronal cell and is released into the bloodstream. These p75 deposits can then be found in urine and tracked over time for increase or decrease in its levels depending on the progression of the disease.

Non-coding RNA
RNA (ribonucleotic acid) is a cell's copy of our genetic information, the DNA. It is important for creation of proteins, the main building blocks of the human body. However, some RNA molecules do not translate into proteins and in most cases have a supportive function (i.e., they help to translate genetic information). These are collectively called non-coding RNAs (ncRNA).

ncRNAs are found in the blood and CSF and are known for their relatively stable levels. This is a useful feature for a potential biomarker as even small deviations can inform us about unusual activity. Researchers are now on the lookout for a number of different ncRNAs that would allow us to track disease progression by observing levels of the specific ncRNAs as the disease progresses.

Inflammatory mediators
Mediators of inflammatory response, such as C-reactive protein (CRP), show the amount of inflammation in an individual's body. It is measured from the blood and high levels often indicate a long-term disease or an infection. Research suggests that higher levels of CRP in people with MND are linked with faster progression of the disease. However, as CRP (and other inflammatory mediators) is in itself a biomarker for inflammation and its reliability for MND is still being researched, it is important to use it in addition to other measures.

Neuroimaging biomarkers

As MND is a neurological disease, it is important to look at the centre of the nervous system – the brain. This is done by using various imaging methods that look at the brain structure (i.e., what the brain looks like) and its functioning (i.e., how the brain works). Examples of such imaging methods include magnetic resonance imaging (MRI), functional MRI (fMRI), magnetoencephalography (MEG), or diffusor tensor imaging (DTI).

Findings from neuroimaging studies revealed that, in MND, some regions of the brain are slightly atrophied (i.e., decreased in mass due to cell death) when compared to brain scans of healthy individuals.

However, the connections that allow different brain regions to communicate show increased activity in people with MND. This increase in connectivity is more evident in people with a more rapid disease progression, which makes neuroimaging a promising candidate for tracking MND.

Muscle measurement

Neuronal death in MND results in impaired communication between the nerves and muscles. This change in electrical activity causes the affected muscles to twitch, which is one of the first symptoms people with MND may notice. Measuring electrical activity in the affected muscles can help with a fast and more straightforward diagnosis.

The standard technique for detecting muscle fasciculations (i.e., muscle twitches) is **electromyography (EMG)**. During this procedure, a fine needle is inserted into the muscles and their electrical activity is recorded. A potentially more efficient alternative, **confocal microscopy**, is currently being investigated. In this procedure, a small probe is placed on the surface of a muscle and its electrical activity can be observed via a specialised microscope in real time. However, as both of these procedures are invasive and quite painful, other techniques are also being looked at by healthcare researchers.

One of the solutions is to use **ultrasound**, which collects information on malfunctions in the electrical activity of a muscle. This procedure is non-invasive and painless and its results are comparable to EMG. Alternatively, researchers are currently testing **surface EMG**, which uses electrical sensors that are placed on the skin.

Finally, magnetic resonance imaging (MRI) of the muscle that is undergoing denervation has started to provide patterns of muscle atrophy linked to development of MND. While MRI is traditionally used to investigate neurological structures, researchers are currently trying to identify signatures of neuromuscular impairment specific to MND. These signatures could be used to monitor the disease and eventually determine response to treatments.

Combination of biomarkers

While the ultimate goal is to find a biomarker that would allow us to detect and track MND with a simple test, the best approach at the moment is to use a combination of various biomarker measurements, most of which are listed above.

3: How do I find out more?

Acknowledgements

We are grateful to Dr Andrea Malaspina for his helpful comments and valuable insight and reviews during the compilation of this information sheet.

Further information

You may find these information sheets from the MND Association helpful:

E – *Research we fund*

We also provide the following guides:

Living with motor neurone disease – our main guide to help you manage the impact of the disease

Caring and MND: support for you – comprehensive information for unpaid or family

carers, who support someone living with MND

Caring and MND: quick guide – the summary version of our information for carers.

You can download most of our publications from our website at **www.mndassociation.org/publications** or order in print from the MND Connect helpline, who can provide further information and support.

MND Connect can also help locate external services and providers, and introduce you to our available services, including your local branch, group, Association visitor or service development manager.

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We welcome your views

Your feedback is really important to us, as it helps improve our information for the benefit of people living with MND and those who care for them. If you would like to provide feedback on any of our information sheets, you can access an online form at: **www.surveymonkey.co.uk/r/infosheets_research**

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Last revised: March 2021