M.E. (myalgic encephalopathy or encephalomyelitis) is a complex multisystem disease with a wide range of disabling symptoms.

M.E. RESEARCH SUMMARY

INTRODUCTION

This leaflet provides a summary of what biomedical research is telling us about M.E. It considers key symptoms, common triggers, and explains how various aspects of disease pathology could be linked to specific symptoms. All references for the research mentioned below, along with more detail, can be found in the ME Association's Clinical and Research Guide and in the research reviews that are available free from our website.

Key Symptoms

M.E. is diagnosed following a significant reduction in pre-illness activity levels and an inability to return to normal function. The most important **diagnostic symptoms** are:

- Post-exertional malaise/symptom exacerbation (PEM) – often with a delayed impact, lasting days or weeks before function is restored. PEM can also trigger a relapse;
- Activity-induced muscle fatigue – precipitated by trivially small exertion (physical or mental) relative to the patient's previous activity tolerance;
- Cognitive dysfunction – problems with short-term memory, concentration, word-finding;
- Sleep problems – sleeping too little or too much, vivid dreams, unrefreshing sleep;
- Ongoing flu-like symptoms – including sore throats and enlarged glands, fever-like sweats, lethargy;
- Orthostatic intolerance – problems with pulse and blood pressure control leading to feeling faint/dizzy when upright.

Other common symptoms include: Disturbed thermoregulation (temperature control), sensory disturbances including paraesthesia (abnormal skin sensations), photophobia (sensitivity to light) and hyperacusis (sensitivity to noise), headaches, shakiness, balance problems, nausea, gastrointestinal problems, alcohol intolerance and chemical sensitivities, recurrent sore throats, shortness of breath, vision problems.

Comorbidities

A number of other medical conditions and symptoms appear to be more common:

- Fibromyalgic-type pain.
- Atypical facial pain and temporomandibular jaw dysfunction.
- Gynaecological conditions - such as pelvic pain unrelated to menstruation, endometriosis and a premenstrual exacerbation of symptoms .
- Hypermobility syndromes - such as Ehlers-Danlos Syndrome (EDS).
- Interstitial cystitis/bladder pain syndrome.
- Gastrointestinal complaints - including irritable bowel syndrome.
- Migraine type headaches.
- Postural Orthostatic Tachycardia Syndrome (POTS) – an abnormal increase in heart rate after sitting or standing, which occurs to compensate a drop in blood supply to the brain, resulting in dizziness and/or fainting, along with other symptoms such as fatigue, headaches and shaking.

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Predisposing and Triggering factors

There is no definitive evidence that can explain why people develop M.E. Factors that seem most likely include:

- A genetic predisposition – which may explain why more than one family member can be affected
- An infection – bacterial or viral
- Trauma – physical or emotional
- Exposure to toxins – including mould and pesticides
- Vaccination

Key research explanations for symptoms and disease pathology

Blood and Plasma abnormalities

- Red blood cell morphology - A recent study from America showed that red blood cells from ME/CFS patients are 'stiffer' and less able to change shape (called deformability) in order to squeeze through small capillaries. This suggests blood flow and oxygen supply to cells may be reduced in ME/CFS. This study was the subject of an **MEA research review**.

- Plasma factor - Preliminary unpublished studies from several independent groups have now found that a factor in the blood plasma (a component of the blood that doesn't include red blood cells) can affect cell metabolism in ME/CFS and that the effect can be transferred to healthy cells. They found that adding plasma from ME/CFS patients to healthy control cells made them increase their oxygen consumption, indicating the mitochondria were working harder. The factor in the blood responsible for these changes is yet to be identified.

- 'Nano-needle' test – In 2019, Dr. Ron Davis from America presented results from a pilot-study testing electrical impedance (ability of a current to pass through cells) in ME/CFS and healthy cells in plasma. He found that putting the cells under 'stress' and making them work harder resulted in a dramatic change in signal. It's as though the cells were unable to keep up with the added demand put on them. Interestingly, when plasma from ME/CFS patients was applied to healthy control cells, the same signal occurred. Suggesting a factor in the plasma was affecting the cells functioning.

Cardiac Function

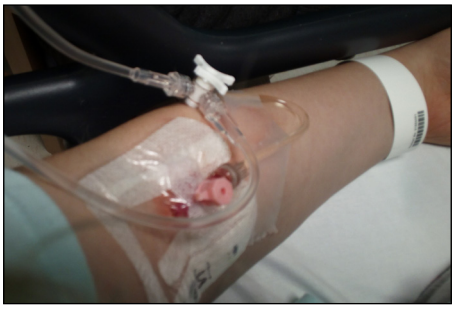
- Some studies have found results suggesting low cardiac output as an explanation for poor physical stamina and chronic fatigue (as a symptom).

- There is also some evidence of hypotension (low blood pressure), especially on standing, which could explain symptoms such as fatigue, dizziness, cognitive issues, tremors and nausea.

Genetics

- Several gene polymorphisms (variations in DNA sequence) have been identified, which are involved in various processes such as immune modulation, oxidative stress and energy metabolism.

- Under and over-expression of certain genes and miRNAs (small



molecules that regulate gene expression) may explain some symptoms and also account for an increased susceptibility to developing M.E. They also represent potential biomarkers for diagnosis and drug treatment targets. Recent findings from Prof Moreau et al. found that miRNAs might be used to place patients into subgroups.

Immunological Dysfunction

- Activated immune system – studies have shown cytokine-mediated, low-level immune system activation, in the blood and cerebrospinal fluid. This results in low-grade inflammation and a general 'sickness response', involving decreased appetite, wanting to sleep a lot and flu-like malaise and pain. Several studies have demonstrated altered levels of inflammatory markers, called cytokines, and activated immune cells, such as lymphocytes. ME Biobank researchers recently found highly increased levels of a type of immune cell called MAIT (Mucosal Associated Invariant T-cell) cells in severely affected patients. The study was the feature of an **MEA research review**.

- Poor cellular function – reduced Natural Killer (NK) cell activity is

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a common research finding. NK cells are a type of white blood cell that comprise part of the immune system and act like security guards, circulating round the body looking for potential threats. However, ME Biobank researchers recently reported no differences in NK cell number and function in patients compared to controls. The study was the feature of an **MEA research review**.

- Autoimmune component – some studies have found activated T- and B-cells, as well as an increased incidence of autoantibodies (immune cells, that attack tissues of your own body, instead of targeting foreign cells, such as bacteria).

Metabolomics

- Recent studies have found abnormalities in several metabolic (chemical) pathways, particularly those involved in glucose metabolism suggesting that there may be problems in converting glucose to energy.

- Other findings point towards a redox imbalance and oxidative stress (where cells are overburdened with toxic by-products from metabolic reactions and don't have enough antioxidants to clear them), which may lead to a lack of oxygen in cells.

Microbiome

- Researchers are currently investigating the role of the microbiome (the collection of different types of microbes, such as bacteria in the gut), with findings indicating gut dysbiosis (an imbalance of gut flora – not enough beneficial bacteria and an overgrowth of bad bacteria). This might contribute to general inflammation and to symptoms like fatigue and gastrointestinal symptoms.

Mitochondria, cellular bioenergetics and exercise physiology

- There is growing evidence of mitochondrial dysfunction. Mitochondria (often called the powerhouse of the cell) are specialised structures responsible for the production of most of our cellular energy.

- Research suggests problems in energy metabolism pathways, such as functional impairments involving an enzyme (a type pf protein that acts as a catalyst for chemical reactions in the body) called pyruvate dehydrogenase and impairments in the activation of another enzyme called AMPK, leading to impaired glucose uptake.

- Researchers from Newcastle University reported cellular bioenergetic abnormalities. A number of measures of mitochondrial function were found to be affected, but in particular, maximal respiration was found to be lower. This suggests that when the cells experience physiological stress they are less able to elevate their respiration rate to fulfil cellular energy demands.

However, the same research group in 2019 demonstrated that the activity of the enzyme complexes within the mitochondria are functioning normally. This suggests the abnormalities in energy production previously observed might be caused by something upstream of the mitochondria and not represent problems with the mitochondria themselves. A recent MEA review considered all the evidence for the **role of mitochondria in ME/CFS**.

- Muscle biopsies have shown evidence of mitochondrial degeneration, deletions of mitochondrial DNA (DNA, located inside the mitochondria, which is inherited from your mother) and reduction of mitochondrial activity.

- A number of other muscle abnormalities have been reported, including defects in muscle energy metabolism, changes in muscle fibre types and demonstrating PEM using repetitive isometric quadriceps exercise testing. These findings demonstrate that muscle symptoms cannot be due to inactivity/ deconditioning.

- Exercise physiology research has demonstrated that a two-day cardiopulmonary exercise test (CPET) can objectively confirm the presence of PEM and could be used as a diagnostic test. This testing method has determined that PEM cannot be due to inactivity or deconditioning.

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Neurology and neuroendocrinology

■ Neuroinflammation – several studies support the presence of neurobiological and spinal fluid abnormalities, some of which are consistent with low level neuroinflammation. A recent study from America found increased temperature inside the brains of ME/CFS patients, as well as increased levels of metabolites, including lactate and choline.

■ Central Nervous System – defects have been found in the basal ganglia pathways (areas of the brain which are extremely sensitive to cytokines). Post-mortem research has also found dorsal root ganglionitis (inflammation in a part of the peripheral nervous system). Abnormal microglia activation (immune cells in the brain) have been found in ME/CFS, a marker of inflammation.

■ Cerebrospinal fluid – studies have shown abnormalities in proteins and white blood cells.

■ Neuroimaging – studies have demonstrated a number of structural and functional abnormalities, including differences in the volume of white and grey matter in the brain, reduced cerebral blood flow and neuroinflamation. This could help to explain symptoms of cognitive dysfunction, as well as pain.

■ Autonomic nervous system (ANS) dysfunction – studies have shown disturbances in the autonomic regulation of cardiovascular reflexes in a subgroup of patients. POTS (Postural orthostatic tachycardia syndrome – represented by an abnormal increase in heart rate upon sitting or standing) is often also diagnosed or Neurally-mediated hypotension. The ANS also controls circulation, which may help to explain why patients experience problems with cold extremities, and temperature regulation. ANS dysfunction may also explain why irritable bowel and bladder symptoms are very common.

■ Hypothalamic-pituitary-adrenal (HPA) Axis – studies have found disturbances involving the HPA axis, mainly demonstrating defects in the output of the hormone cortisol from the adrenal glands. This could explain key symptoms such as fatigue, sleep dysfunction and also temperature regulation.

Advancing M.E. research

We need:

■ Much larger studies with higher numbers of participants, in order to see more definitive research and the removal of any false positives.

■ Well-defined patient cohorts and greater use of sedentary and other relevant controls.

■ To identify subgroups. There is a general consensus amongst researchers that there are several subgroups of patients which present with slightly different symptoms and pathologies. These need to be defined in order to study them separately.

■ To use new investigative techniques – including genomics, metabolomics and proteomics to find out what is happening at a cellular level.

■ Collaboration between different areas of research in order to see the 'whole picture'.

■ **Funding!** The Medical Research Council (MRC) regards ME/CFS as a research priority and issued a highlight notice in 2011 to encourage research applications – especially in relation to immune system dysfunction and neuropathology. Unfortunately, very little had happened despite this central encouragement.

In January 2020, a major new application from the ME/CFS Biomedical Partnership was submitted to the MRC and National Institute of Health Research (NIHR) that would result in a genetics study on 20,000 people with the condition. This £3.5million bid could provide answers to important questions about causation. The MEA has been involved in this initiative since the beginning and in all the discussions with the MRC/NIHR in the last couple of years. We hope to share good news about the application in the coming months. Please consider registering your interest with this project by visiting the **ME/CFS Biomedical Partnership website**. However, in general, research remains severely underfunded in the UK with most of the contribution still coming from the small charity sector. In recent years, the **MEA Ramsay Research Fund** has invested over £1million in biomedical research and continues to seek good quality applications.

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Conclusions

The most widely accepted model for M.E. is that it is a complex, multisystem disease which is triggered by an immune system stressor, commonly an infection, in a genetically predisposed individual. The illness is then perpetuated by interaction of various changes in the brain, muscles, immune and endocrine (hormone) systems.

Until we have a better understanding of the underlying disease pathways, and the various clinical and pathological sub-groups, progress in developing a reliable diagnostic test and an effective form of drug treatment is likely to remain slow. However, important clues are emerging, and new types of drug treatment are being assessed on the basis of these abnormalities. And there is movement on the central funding front with groups like the CFS/ME Research Collaborative (CMRC) working to advance the case for M.E. research investment.

Research provides the best chance we have of improving the lives of people affected by this awful disease. There is good reason to hope that M.E. research will be taken seriously in the UK and that effective forms of treatment will eventually emerge.

Further information

For more information please refer to our new factsheets below:

M.E. Factsheet: What you need to know about M.E.

Ramsay Research Fund Factsheet: Explains the research we are funding and how to apply for research grants.

■ To read about ME/CFS in more detail (symptoms, diagnosis, research findings and management) purchase a copy of the **ME Association's Clinical and Research Guide**. This book is fully referenced and written and updated each year by Dr Charles Shepherd and Dr Abhijit Chaudhuri. We are able to offer free hard copies to health professionals, and a Kindle version is now available on Amazon.

■ The ME Association funds biomedical research via The Ramsay Research Fund. You can read all about the research we are currently funding, as well as the research we have helped fund, by visiting the **research section** on our website.

The guide is available in print or on Kindle. Visit **Amazon Smile** or **Amazon** for more information and to make a purchase.

How you can help

Please help us to build on our success and continue to expand our vital work. One day we will find the cause of M.E. and have an effective form of treatment. And with your help, that day could come much sooner.

If you would like to help the Ramsay Research Fund invest in even more biomedical research, please donate now:

■ with either a single **online** donation,

■ by cheque (made payable to: The ME Association Ramsay Research Fund) to:

The ME Association, 7 Apollo Office Court, Radclive Road, Gawcott, Bucks MK18 4DF.

■ by card donation over the phone to our head office (01280 818964)

Or, if you would like to fundraise for the Ramsay Research Fund, please start your online giving page, **here**.

How to apply for a research grant

We would encourage any researcher to first contact our medical adviser Dr Charles Shepherd (via **admin@meassociation.org.uk**) for an informal discussion.

If you would like to submit an outline proposal for consideration, please do so by providing the necessary information on **our research proposition form** and returning it to us as soon as possible.
The next stage in the process will require submission of a formal grant application, but this should not be completed until your outline proposition has received approval. We aim to reply to all propositions within four weeks of receipt.

Grant decisions are based on the guidelines produced by the **Association of Medical Research Charities** and would normally include both an internal and external peer review of all formal grant applications.

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The ME Association:

- Provides information on M.E. and campaigns on issues such as research, the NICE guideline, NHS service provision and care
- Provides support through our ME Connect helpline, ME Essential members magazine and our website and social media
- Funds biomedical research – including the UK ME/CFS Biobank which is managed by an expert team at the London School of Hygiene and Tropical Medicine – through the Ramsay Research Fund
- Is a member of the Forward ME Group of charities and patient representatives that is chaired by the Countess of Mar, and the CFS/ME Research Collaborative, chaired by Professor Stephen Holgate, which aims to raise the profile of M.E. and attract greater research investment

Further information:

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Ramsay Research Fund Factsheet

ME Association: ME/CFS/PVFS An Exploration of the Key Clinical Issues

ME Association: An Index of Published ME/CFS Research

ME Association: Website

ME Association: Facebook **and** Twitter **and** Instagram

The ME Association website shop:

You can download leaflets and buy gifts from our website shop or by downloading and completing our Order Form. If you are a member of the ME Association, you will receive an order form with your quarterly magazine.

The following literature is available to download or order:

Medical Management
Leaflets about the medical management of ME/CFS – 51 topics covered.

ME Connect
Useful leaflets based on the concerns expressed by people who have used our ME Connect helpline.

Diet & Nutrition
Our dietary advisers provide key information to help you maintain a healthy diet even when ill.

General Information
Guides to going to university and travel insurance – with other great leaflets.

Fundraising Leaflets
You'll be welcome to download our free fundraising leaflets.

Benefits & Social Care
Includes guides to Universal Credit and PIP and obtaining Social Care.

'To Whom It May Concern' letters
For when you need to explain to others how M.E. can affect your ability to do things.

Our quarterly **ME Essential** magazine goes out to all members

If you would like to receive it regularly, please phone our office on 01280 818 963 or email:
admin@meassociation.org.uk