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.

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

Predisposing and Triggering factors

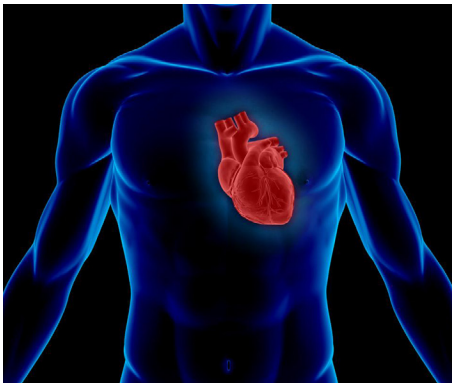
There is no definitive evidence that can explain why people develop M.E. Factors that seem most likely include:

- 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

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.

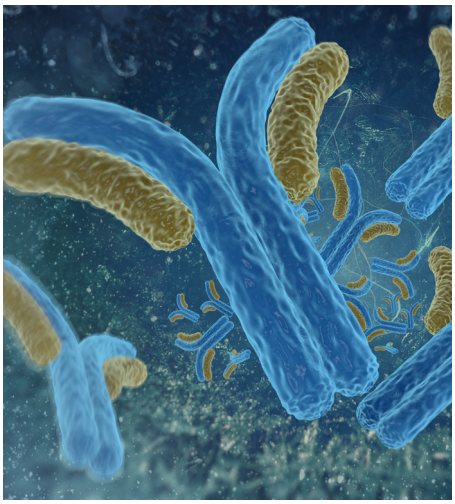


Genetics

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



- 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.

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.

Muscle research: mitochondrial dysfunction, 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.

- 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.

- 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 (adenosine monophosphate-activated protein kinase), leading to impaired glucose uptake.

- Recent research from Newcastle University presented at the 2018 CMRC conference have also shown reduced mitochondrial function.

- 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.

Neurology and neuroendocrinology

- Neuroinflammation – several studies support the presence of neurobiological and spinal fluid abnormalities, some of which are consistent with low level neuroinflammation.

- 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).

- 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! One of the biggest things holding back our search for knowledge and ways to tackle this disease is a lack of investment. The ME Association Ramsay Research Fund has invested over £1m in biomedical research, but charity investment is not enough. We need the Medical Research Council and National Institute of Health Research to provide much greater funding if we are to build on pilot studies and produce the kind of research that will improve outcomes for people with M.E.

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.

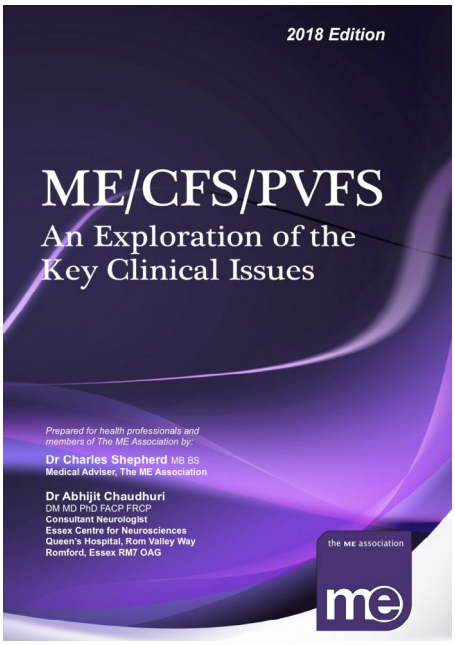
Research provides the best chance we have of improving the lives of people affected by this awful disease. There is good reason to hope that M.E. research will be taken seriously in the UK and that effective forms of treatment will eventually emerge.

Further information

For more information please refer to our new factsheets below:

M.E. Factsheet

Ramsay Research Fund Factsheet



- 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.

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

If you would like to receive it regularly, please phone our office on 01280 818 968

or email: **admin@meassociation.org.uk**