What do we know about the causes of ME/CFS?

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Background

The underlying cause of ME/CFS is subject to much uncertainty and medical debate. This is one of the reasons why doctors have differing views on how the condition should be managed.

At the one end of the spectrum of medical opinion are those – myself included – who believe that ME/CFS is caused by a physical disease process that results in a number of symptoms affecting different parts of the body.

This has now been shown to involve the brain and central nervous system, muscle, immune and endocrine systems.

Mental health symptoms, where they occur, are a consequence and not a cause of ME/CFS. They are a very understandable result of the practical difficulties and emotional stresses of living with a long-term and very disabling illness.

In the middle – and representing possibly the majority of medical opinion – are those who believe that ME/CFS involves a combination of physical, psychological and social factors: the biopsychosocial model. This model assumes that, while ME/CFS is often triggered by a physical stressor such as an infection, persisting ill health is largely maintained by maladjusted behavior and unhelpful illness beliefs.

At other end of the spectrum are doctors who believe that ME/CFS is a pure psychiatric disorder – where symptoms have no underlying physical cause. A few doctors still take the view that ME/CFS does not even exist, or is just a form of atypical depression or hysteria.

This situation is clearly unsatisfactory and unhelpful. Unfortunately, it is likely to continue until medical research has produced replicated studies big and good enough to convince those in doubt that a physical disease process is in fact taking place.

Defining ME/CFS for Clinical and Research Purposes

The medical profession decided to rename and redefine what was known as ME in the mid/late 1980s as chronic fatigue syndrome (CFS).

Research into both cause and treatment therefore moved to include a much broader group of people with some form of chronic fatigue. And, while the much broader Fukuda definition of CFS

includes many people who have Ramsay or London-defined ME, it does not include everyone with ME. So there are people with ME who also meet criteria for CFS – as well as others who do not.

Most research into the cause and treatment of ME and CFS now uses patients who have one of the research definitions for CFS – normally the Fukuda definition, which originated at the Centers for Disease Control in America.

There are other more appropriate research definitions available, including the Canadian Consensus Criteria, which is occasionally used along with the Fukuda – as we are doing at the UK ME/CFS Biobank. However, very little research has been carried out using people who have ME as described originally by Dr Melvin Ramsay, or in the London Criteria – a research definition I helped to produce and which was updated in 2014.

Using Fukuda-defined CFS is rather like taking everyone with any type of arthritis – autoimmune, inflammatory, infective, 'wear and tear' osteoarthritis, etc – and then saying that they have a 'chronic joint pain syndrome', researching this group without dividing them into the different sub-groups of arthritis, and finally using the results to conclude that everyone with chronic joint pain has the same cause and requires the same treatment. This is clearly not the case.

So any conclusions about research into causation of ME/CFS (a compromise term that includes everyone with either ME or CFS), or clinical trials into treatment, have to carry a serious note of caution – because the research has been carried out on a very diverse group of patients who have differing clinical presentations and almost certainly have different disease pathways.

On a more positive note, there is now growing agreement across the spectrum of medical opinion that the term CFS covers far too wide a group of clinical presentations and disease pathways. Consequently, we must now start to look at how the various sub-groups of patients who come under the messy ME/CFS umbrella can be identified.

Is ME/CFS a Three-stage Illness?

Despite all the problems relating to definition and patient selection, there is a considerable degree of agreement emerging that we are dealing with a three-stage process in ME/ CFS. This involves specific factors that predispose, precipitate and perpetuate the various symptoms.

Predisposing Factors

As with many chronic diseases - arthritis, cancer, heart disease etc - it appears that genetic factors play a role. So while ME/CFS is not a genetic disorder in the sense that it can be passed from parent

to child, there is growing evidence that some people have a genetic make-up that increases the risk of ME/CFS developing when a trigger factor, such as an infection, occurs at a particular time in their life. This genetic predisposition may also help to explain why there are families with more than one member who has ME/CFS.

New research on brain structure and function suggests that infections, or events prior to the onset of ME/CFS, may help to prime or activate immune system cells in the brain called microglia. When faced with another infection, this priming of the microglia may then make some people more vulnerable to developing ME/CFS.

Precipitating Factors

One area where there is a considerable degree of medical agreement relates to what triggers, or precipitates ME/CFS. Most people with this illness pre-date the onset of their symptoms to an infection – normally viral but sometimes bacterial – from which they 'fail to recover' and continue to have 'flu-like symptoms', along with the very characteristic muscle and brain symptoms that are associated with ME/CFS.

Other types of immune system stressors – vaccinations, trauma, pregnancy, surgery – can occasionally trigger ME/CFS. It also appears that stress – physical, mental, emotional, or a combination of all three – around the time of a triggering infection, or during the recovery period, can be an important co-factor in determining whether the body makes an appropriate response.

Perpetuating Factors

This is where the situation becomes far more uncertain, and where disagreements emerge in relation to what then perpetuates, or keeps the illness going.

Those who believe that ME/CFS is a mental health or somatoform disorder argue that symptoms are largely prolonged by what are called abnormal illness beliefs and behaviours, along with physical deconditioning. Any physical abnormalities are caused by factors such as sleep disturbance and inactivity.

Those who adhere to the physical model of causation believe that ME/CFS is perpetuated by a complex interaction involving changes to the way in which the brain, muscle, immune and endocrine systems respond to the triggering viral infection, or other immune system stressor. All the key abnormalities that have been reported so far are summarised later in this article.

- **Brain abnormalities**

Using a variety of ways of investigating brain structure/anatomy and function in ME/CFS, there is now sound evidence of significant abnormalities involving the brain and central nervous system.

One of the most consistent reported abnormalities involves what is called the autonomic nervous system (ANS). This is a part of the brain and nervous system that is not under conscious control and which sends 'speeding up' or 'calming down' messages to vital organs such as the heart, bowel and bladder.

This finding is of practical importance because it helps to explain symptoms such as orthostatic hypotension, where blood pressure falls on standing and may cause fainting, and postural orthostatic tachycardia syndrome (POTS) – where the pulse rate rises on standing.

The autonomic nerves also control the size of tiny blood vessels supplying the skin, which may help to explain why some people with ME/ CFS have cold hands and feet. ANS dysfunction may further explain why irritable bowel and bladder type symptoms are very common in ME/ CFS.

Brain scans have demonstrated a range of abnormalities including changes in blood flow to key parts of the brain, which could help to explain the cognitive dysfunction (= problems with short-term memory, concentration, etc), as well as other brain-related symptoms such as poor temperature control and pain.

New research from Japan has demonstrated abnormalities that are consistent with low-level inflammation in the brain, possibly as a result of immune system activation. And a new study from Stanford University in America has demonstrated a reduced amount of white matter, with a specific white matter abnormality in the right hemisphere of the brain called the arcuate fasciculus.

Post-mortem research carried out here in the UK, and partially funded by the MEA Ramsay Research Fund, has found an abnormality called dorsal root ganglionitis (= inflammation of the dorsal root ganglia) in a small number of cases. This is a part of the peripheral nervous system that lies just outside the spinal cord and helps to relay messages about sensation and pain back to the brain.

- **Muscle abnormalities**

Abnormalities involving skeletal muscle biochemistry in ME/CFS, where there's an abnormally prolonged production of lactic acid following exercise in some people, were first described over 30 years ago in *The Lancet*. This research, in which I was involved and used my own leg muscle, was carried out in Oxford. It examined what happened at a biochemical level during exercise using

magnetic resonance spectroscopy (MRS).

Since then, structural and functional abnormalities involving the mitochondria – a key part of the cell where nutrients are converted into an energy-carrying molecule called adenosine triphosphate (ATP) – have been reported in a number of research studies.

The MEA Ramsay Research Fund is currently co-funding a further study into mitochondrial function in ME/ CFS at the University of Liverpool. The Fund has also been supporting research into mitochondrial function at the University of Newcastle.

- **Immune system abnormalities**

A wide range of immunological abnormalities have been reported in ME/CFS. These involve all the different parts of the immune system: natural killer cells, antibodies, auto-antibodies and cytokines. However, none of these are consistent or robust enough to regard them as diagnostic, to provide a direct link to symptoms, or to be useful in relation to management with drugs that can modify the immune system response.

Of particular interest are abnormalities involving cytokines. These are immune-system chemicals that are produced in response to any type of infection and which result in a range of symptoms that form part of the body's normal sickness response. These include loss of appetite, wanting to sleep more than normal, aches and pains in muscles and joints.

This model of illness, in which an infection triggers an inappropriate or protracted immune-system response, is one that the MEA has proposed for many years. Further support comes from new research presented at the 2014 CFS/ME Research Collaborative conference in Bristol which has found that people who are given interferon alpha (a type of cytokine) as a treatment for hepatitis C develop an ME/CFS-like illness as a side-effect.

Our Ramsay Research Fund is currently co-funding new research into immune system function at the Universities of Newcastle and Northumbria.

One of the most promising areas of research in relation to treatment is looking at ways in which drugs that affect the immune system – such as Rituximab – could be a safe and effective form of treatment for ME/ CFS.

- **Infection**

Although a range of infections are known to trigger ME/CFS, most research that has investigated

infection has not supported a role for persisting viral infection – as happens with hepatitis C or with HIV infection and AIDS. However, there is some evidence from Dr John Chia's research group in America of persisting enteroviral infection being present in some people with ME/CFS.

There is also conflicting research evidence regarding a role for reactivated viral infection with human herpes virus 6 (HHV-6) and Epstein Barr virus – which causes glandular fever. These are both herpes virus infections that remain dormant in the body after an initial infection and which can be reactivated as a result of immune system activation.

- **Endocrine abnormalities**

One of the most consistent research abnormalities to be seen in ME/CFS involves what is termed a down- regulation of the hypothalamic- pituitary-adrenal (HPA) axis. The hypothalamus and pituitary are tiny glands inside the brain that play a key role in the control and production of hormones elsewhere in the body.

In the case of ME/CFS, there seems to be a defect in the output of the hormone cortisol from the adrenal glands, which sit above the kidneys. This lowered level of cortisol (= hypocortisolaemia) could be related to symptoms such as fatigue and low blood pressure.

The hypothalamus also acts as the body's thermostat in relation to appetite, sleep and temperature control – all of which are affected in ME/CFS.

Conclusions

Linking all these abnormalities together helps to explain why ME/CFS is often described as a complex multisystem disease. But the only way that firm conclusions about causation are going to be reached is through well-designed research studies using carefully selected patients.

Until we have a better understanding of the underlying disease pathways in ME/CFS, and the various clinical and pathological sub-groups, progress in developing an effective form of drug treatment is likely to be slow.

However, important clues are emerging and new types of drug treatment are being assessed on the basis of these abnormalities. So there is now real hope that effective forms of treatment will eventually emerge.

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More information:

A more detailed summary of current research findings, which is fully referenced to relevant medical papers, can be found in the MEA purple booklet ME/CFS/PVFS: An Exploration of the Key Clinical Issues written and updated by Dr Charles Shepherd, and Dr Abhijit Chaudhuri, consultant neurologist at the Queen's Hospital, Romford, Essex.