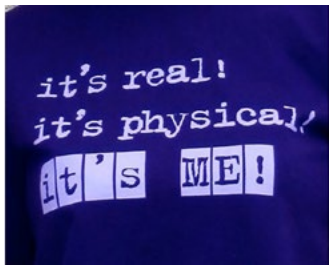


MANAGEMENT FILE

by DR CHARLES SHEPHERD, our medical adviser

This leaflet is a wholly revised version an article which first appeared in the ME Association's quarterly *ME Essential* magazine.
MEA membership costs £18 a year for people living in the UK/BFPO.
For contact details, see foot of this page.

the ME association

February 2020

IS M.E. A NEUROLOGICAL DISEASE?

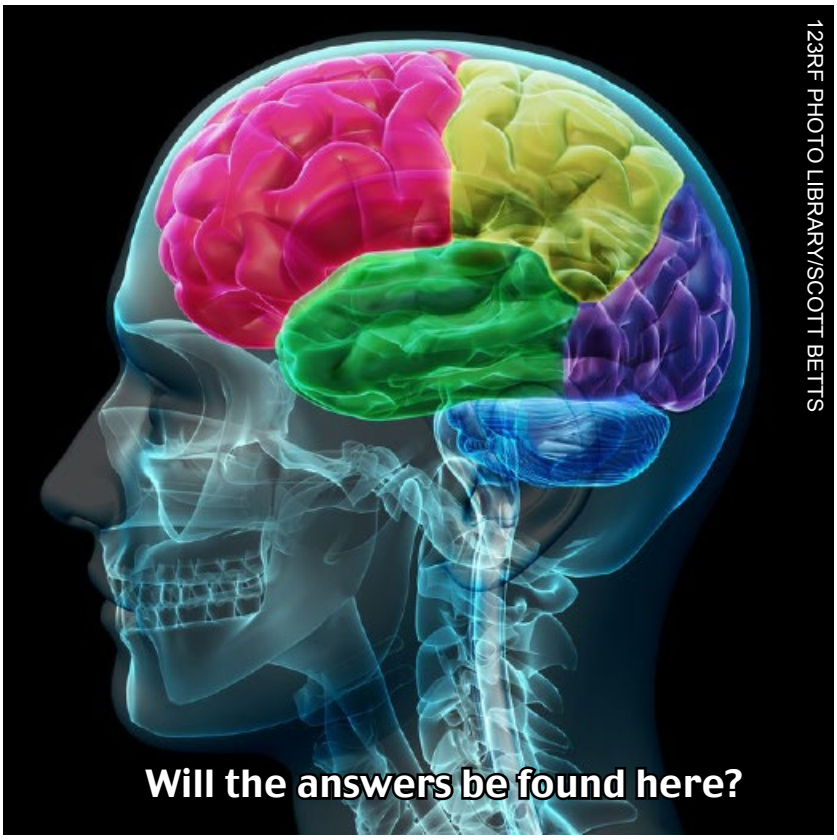
This leaflet summarises all the key clinical, research and political evidence supporting a neurological classification for myalgic encephalopathy/encephalomyelitis (M.E.).

The ME Association position is that myalgic encephalopathy – meaning problems with muscles (myalgia) and with brain function (encephalopathy) is the most suitable name for the disease at this time.

There is no significant or consistent pathological evidence to support the use of the term 'encephalomyelitis' (widespread inflammation of the brain and spinal cord) although the terms 'benign myalgic encephalomyelitis' and 'post-viral fatigue syndrome' have been (and stilll are) used to describe the condition by the World Health Organisation.

This lack of definitive evidence accounts in part for the reluctance of neurology to accept M.E. into its medical discipline. Many doctors still prefer to use 'chronic fatigue syndrome' but this is not a name we support as it does nothing to explain causation and downplays the severity of the condition. It's akin to calling dementia, chronic forgetfulness syndrome!

We believe that myalgic encephalopathy (M.E.) should not be dismissed by neurology, and that neurologists have a key role to play in diagnosis and management, but we also believe that the cause of symptoms may stem from other systems in the body.



Until such time as research determines actual causes for the symptoms, and the name and description of this disease can be better determined, we continue to support a neurological classification.

◆ See our free factsheet for an overview of M.E.: https://tinyurl.com/yxlc46qw

WHAT DO WE MEAN BY NEUROLOGICAL?

Neurological disorders are diseases of the nervous system. These include structural, biochemical or electrical abnormalities in the brain, spinal cord or peripheral nerves that can result in a range of symptoms.

◆ See our free factsheet for a summary of the key research evidence of abnormalities found in M.E.: https://tinyurl.com/rpkkp7z

WHO CLASSIFICATION

'Benign myalgic encephalomyelitis' (M.E.) and Post-Viral Fatigue Syndrome (PVFS) have been recognised as examples of neurological disease by the World Health Organisation (WHO) since 1969.

The WHO lists all known diseases in the International Classification of Diseases (ICD), using a system of diagnostic codes that are recognised by the UK and other member states.

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In ICD-10, M.E. and PVFS were both classified as neurological disorders in section G93.3, under 'Other disorders of the brain', in Chapter VI 'Diseases of the nervous system'. CFS (chronic fatigue syndrome) was not listed specifically but was indexed to this section.

ICD-11 was launched in January 2020 and will replace ICD-10 when it is finally implemented in January 2022. ICD-11 lists both ME and CFS in Chapter 08, 'Diseases of the nervous system'. They appear under 'Other disorders of the nervous system' in section 8E49, as inclusions in the entry for PVFS.

THE UK GOVERNMENT POSITION

Government ministers have repeatedly made it clear that their departments accept the WHO classification of ME/CFS as being neurological in origin.

In 2010, the office of the **UK's Chief Medical Officer** confirmed:

"The Department's view is that it is important to recognise that CFS/ME is a genuine and disabling neurological illness and health professionals must recognise it as such."

In 2011, **Paul Burstow, Minister for State, Department of Health**, said in a debate:

"There is strong international consensus that CFS/ME is a chronic and disabling neurological illness. I want to stress that it is a neurological illness; it is not a mental health problem."

In a written answer provided in 2013, **Minister for Care Services Norman Lamb** stated:

"The World Health Organisation International Classification of Diseases (ICD-10) classifies chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME) under neurological disorders at Reference 93.3 and uses the terms post-viral fatigue syndrome (PVS) and benign myalgic encephalomyelitis. The Department accepts this classification and recognises CFS/ME as a neurological condition of unknown origin."

CLINICAL EVIDENCE OF NEUROLOGICAL DYSFUNCTION

People with M.E. have a variety of neurological symptoms. These include:

- **Alcohol/Drug Intolerance**

Intolerance or sensitivity is not uncommon, especially in relation to drugs such as antidepressants and painkillers that act on the brain and nervous system. Medications may need to be introduced slowly with a low dose that is built up over time.

- **Autonomic Nervous System Dysfunction**

This can produce symptoms such as feeling faint on standing, orthostatic intolerance and postural orthostatic tachycardia syndrome.

- **Cognitive Dysfunction**

Problems with short-term memory, concentration, attention span, information-processing and word-finding ability; often referred to as 'brain fog' by patients.

- **Chronic Fatigue**

Activity-induced fatigue is almost always present and even minor physical and/or cognitive exertion can lead to post-exertional malaise (PEM) and an often-delayed exacerbation of symptoms.

The fatigue in M.E. has similar features to the central (brain) fatigue found in other neurological conditions, such as multiple sclerosis and there may also be similar pathological mechanisms involved – although PEM is thought to be a rather unique and characteristic symptom of M.E.

- **Dysequilibrium**

Problems with balance that may induce feelings of vertigo and nausea.

- **Headaches and Migraines**

Headaches and migraines (sometimes without headache but acute sensitivity to light and/or nausea) are often experienced.

- **Hypothalamic Dysfunction**

Leading to disturbances in temperature control and down-regulation of the hypothalamic-pituitary-adrenal axis controlling the output of cortisol.

- **Neuropathic Pain**

Pain that has a burning, stabbing or searing quality.

- **Sensory Disturbances**

Include loss of sensation, abnormal sensations/paraesthesiae, and increased sensitivity to light, sound and touch.

- **Sleep dysfunction**

Including hypersomnia, fragmented sleep patterns, waking feeling unrefreshed, insomnia, vivid dreams and night-sweats.

- **Tinnitus**

The perception of hearing noises often a ringing in the ears.

- **Other Symptoms**

Some people, especially those with severe aymptoms, may experience more severe neurological symptoms – including atypical seizures (i.e. not epilepsy), blackouts, double vision, loss of speech and loss of swallowing ability (requiring tube-feeding).

RESEARCH EVIDENCE OF NEUROLOGICAL ABNORMALITIES

There is growing evidence of significant abnormalities in the brain, involving both structure and function, as well as neuro-inflammation and biochemical changes. Among the most important findings to date are:

- **Differences in white and grey matter volumes in the brain.**

– Independent MRI (magnetic resonance imaging) studies have demonstrated significant reduction in the volume of grey matter (de Lange et al, 2005; jkOkada et al, 2004) in the outer part of the brain. Okada et al reported that the reduction in grey matter volume in the right prefrontal cortex correlated with the severity of fatigue.

– MRI and voxel-based morphometry (VBM) studies demonstrated an overall reduction in white-matter content in the brains of ME/CFS patients compared to the brains of healthy

subjects that is related to functional status (Barnden et al, 2015; Cook et al, 2001; Finkelmeyer et al, 2018; Zeineh et al, 2015).

– A voxel-based morphometry (VBM) study found significant reductions in white and grey matter volume for CFS patients when compared to controls (Puri et al, 2012). The authors concluded, "…these data support the hypothesis that significant neuroanatomical changes occur in CFS and are consistent with the complaint of impaired memory that is common in this illness."

– Progressive brain changes have been investigated by Shan et al. (2016) using longitudinal MRI in 15 ME/CFS patients and 10 healthy controls. Both groups were scanned twice six years apart on the same 1.5 Tesla scanner. There was a significant decrease in white matter volumes in the left inferior fronto-occipital fasciculus in the ME/CFS group; in healthy controls, there was no change. Regional white matter and grey matter volumes showed significant correlations with ME/CFS symptom scores.

Changes in brain chemicals

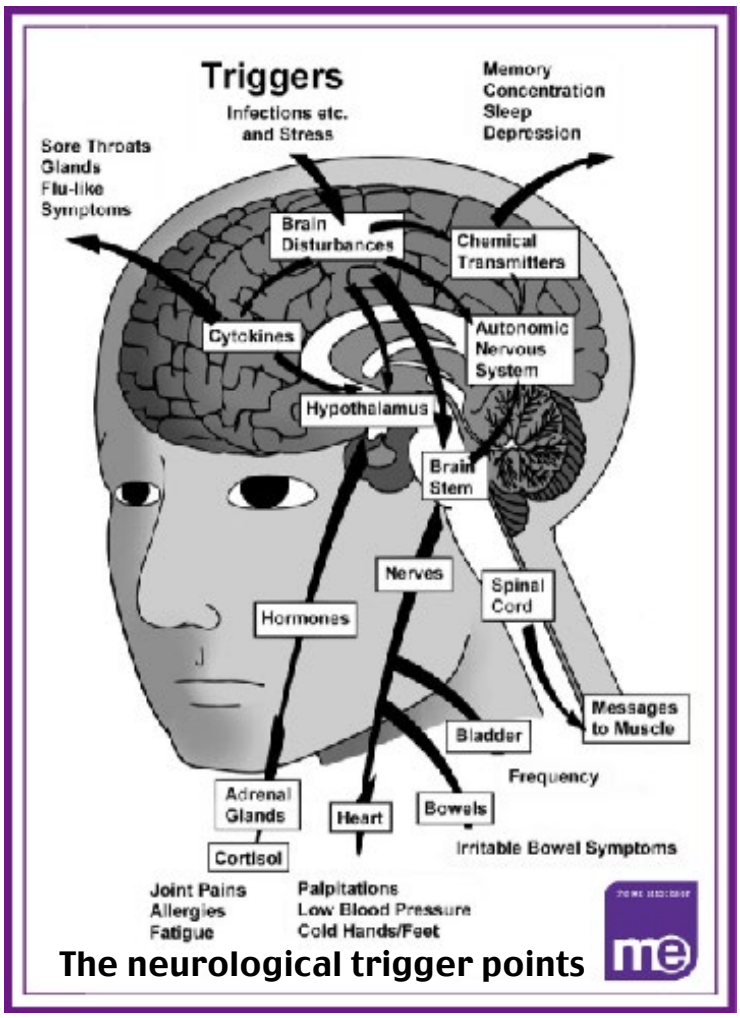
– Changes in the activity of neuro-transmitters, in particular serotonin (Badawy et al, 2003) and dopamine modulation (Georgiades et al, 2003) have been observed.

– Abnormalities involving brain chemicals such as reduced acetylcarnitine uptake (Kuratsune et al, 2002) and raised levels of choline (Chaudhuri et al, 2003; Mueller et al, 2019; Puri et al, 2002)

– Significantly reduced concentration of N-acetylaspartate, a marker for neuronal function, was observed in the right hippocampal region of ME/CFS patients (Brooks et al, 2000).

– Elevated ventricular lactate and decreased cortical glutathione were found in patients with ME/CFS compared to healthy volunteers (Natelson et al, 2017; Shungu et al, 2012).

– Mueller et al (2019) found differences in the levels of Lactate, Choline, myoinositol and N-acetylaspartate in ME/CFS patients compared to controls, using Magnetic Resonance Spectroscopy analysis.



Decreased blood flow in the brain

– Decreased Blood flow (hypoperfusion) has been found in various areas of the brain, including the brain stem (Costa et al, 1995; Natelson et al, 2017; Yoshiuchi et al, 2006).

– Two recent studies observed changes in cerebral blood flow related to fatigue following task-related activity (Boissoneault et al, 2018; Staud et al, 2018).

Changes in cerebrospinal fluid

– Elevations of protein and white blood cells in cerebrospinal fluid (Natelson et al, 2005 & 2017) – an abnormality suggesting immune system dysregulation within the central nervous system.

– Increased levels of ventricular cerebro-spinal fluid lactate (Mathew et al., 2009; Murrough et al., 2010; Natelson et al., 2017).

Neuroinflammation

– A Japanese group have recently demonstrated abnormalities in several areas of the brain that are consistent with neuroinflammation, which was associated with the severity of symptoms (Nakatomi et al., 2014 & 2018).

– Elevated brain temperature, along with differences in levels of key markers of neuroinflammation, were observed in ME/CFS patients compared to controls through MRS analysis (Mueller et al., 2019).

Reduced functional connectivity

– Numerous studies have found objective evidence of cognitive dysfunction through functional neuro-imaging studies. Reduced functional connectivity has been observed in several core neurocognitive areas of the brain, including the brainstem (Barnden et al, 2019; Boissoneault et al, 2018;

Lange et al, 2005; Michiels and Cluydts, 2001; Wortinger et al, 2017; Zinn et al, 2016 and 2018).

Post-mortem research

– A report on the histopathological changes in the dorsal root ganglia of three female patients with ME/CFS concluded that the most remarkable and consistent abnormality was the presence of active inflammation with T8 lymphocytic infiltration in the dorsal root ganglion of one patient and evidence of past inflammation (nodules of Nageotte) in two patients (Cader et al, 2009).

– Ferrero et al (2017) have published a second postmortem report which refers to focal areas of white matter loss, neurite beading and amyloid plaques.

Other findings

– Reduced basal ganglia responsivity, associated with the severity of symptoms (Miller et al, 2014).

– Decreased activation in regions of the frontal lobe (Zinn et al, 2018).

– Structural abnormalities in several areas of the brain (Kimura et al, 2019; Zeineh et al, 2015; Shan et al (2017) demonstrated that differences in brain structure are associated with sleep quality in ME/CFS.

– Evidence of hypothalamic dysfunction – a key part of the brain that regulates a number of body functions including temperature control and hormonal output, in particular the production of cortisol from the adrenal glands (Papanicolaou et al, 2004); and the autonomic nervous system (Freeman, 2002).

WHY DO SOME DOCTORS BELIEVE THAT M.E. IS NOT A NEUROLOGICAL DISEASE?

The NHS defines neurological conditions as 'resulting from damage to the brain, spinal column or peripheral nerves'. This may be why some physicians find it difficult to believe M.E. is a neurological disease because there is no definitive or widely accepted proof of damage to the brain, spinal column or nerves, although there is substantial evidence of brain abnormalities *(see above)*.

While these research findings relating to both structure and function in the brain are important, most of them are not sufficiently consistent or robust enough to indicate that they are directly related to M.E. symptoms. For example, in relation to neuroimaging studies, there are differences in neuroimaging techniques, assessment criteria and methodology between studies, technical limitations and different ways of interpreting and analysing the imaging data.

Because there is currently no definitive biomarker of neurological disease in M.E., this might also explain why some neurologists in particular are reluctant to accept a neurological classification.

And, while it is clear that patients with M.E. present with many neurological symptoms and clinical abnormalities, it is not yet certain what is causing them. There may be explanations other than neurological disease, such as immune system abnormalities, infections or cardiovascular problems.

THE NHS AND THE NICE CLINICAL GUIDELINE

M.E. and CFS are classified under 'disorders of the nervous system' in SNOMED CT (Clinical Terminology), a comprehensive electronic clinical classification system used by the NHS. On the NHS England website, under 'Neurological conditions', M.E is given as an example in the 'Intermittent and unpredictable conditions' category of neurological conditions.

The current 2007 NICE clinical guideline for CFS/ME (CG53) mentions many different potential aetiologies – including neurological, endocrine, immunological, genetic, psychiatric and infectious. The guideline states:

"The World Health Organisation (WHO) classifies CFS/ME as a neurological illness (G93.3), and some members of the Guideline Development Group felt that, until research further identifies its aetiology and pathogenesis, the guideline should recognise this classification. Others felt that to do so did not reflect the nature of the illness, and risked restricting research into the causes, mechanisms and future treatments for CFS/ME."

The 2007 guideline is currently being rewritten; the new version is expected to be published in December 2020 following stakeholder consultation. Unfortunately, despite the acknowledged classification, patients are unlikely to be referred to a neurologist, except possibly for help with diagnosis. Additionally, referral to a neurologist is unlikely to change the treatment or management options received.

Dr Charles Shepherd (Hon Medical Adviser to the ME Association) commented: "The major problem in relation to neurology and M.E. is that the vast majority of UK neurologists (84% in a survey published in 2011) do not believe that it really is a neurological disease.

"This is often based on the view that people with M.E. do not have what are termed hard neurological signs on physical examination and a belief that there is no convincing research evidence of neurological abnormalities being linked to symptoms. Consequently, a significant proportion of neurologists do not want to see patients with M.E., arguing that they should be dealt with by primary care, i.e. by a GP."

The NICE Clinical Guideline CFS/ME (2007): https://tinyurl.com/u9g9jj8

Neurologist Survey: 'Chronic fatigue syndrome: labels, meanings and consequences' by Wojcik et al. 2011: https://tinyurl.com/u5bxmgq

Medical information in this leaflet is not intended to be a substitute for medical advice or treatment from your own doctor.

The ME Association recommends that you always consult your own doctor or healthcare professional about any specific problems.

We also recommend that any medical information provided by The MEA in this leaflet is, where appropriate, shown to and discussed with your doctor or dentist.

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