**ME/CFS: The importance of making an early and accurate diagnosis**

**Introduction**

ME/CFS (myalgic encephamlomyelitis/chronic fatigue syndrome) is a complex multisystem disease that has a population prevalence of at least 0.2% to 0.4%. So it probably affects between 2 and 4 per 1,000 of the population and up to 250,000 people in the UK. There is a wide range of severity at all stages of the illness. Around 25% are severely affected at some stage – being house-bound or bed-bound – and this can create additional challenges when making a diagnosis.

Many people experience a long delay in obtaining a diagnosis. A 2016 MEA website survey involving 656 respondents found that of those who were diagnosed by a doctor:

* only 18 % were diagnosed within six months of the onset of symptoms
* 15% waited between 7 and 12 months
* 17% waited between 13 and 24 months
* 26% waited between 2 and 5 years
* 19% waited more than 5 years

The remainder could not remember, or had never received confirmation of the diagnosis from a doctor.

Fatigue is a very common symptom and some people with chronic fatigue are being misdiagnosed with ME/CFS when they have another, sometimes perfectly treatable, explanation. ME/CFS is a distinct clinical entity with a characteristic set of core symptoms. It should not be used as a diagnostic label for people with unexplained chronic fatigue.

**? Boxed: The information and guidance contained in this leaflet is a summary of all the key issues relating to making an early and accurate diagnosis of ME/CFS. More detailed information on clinical assessment, differential diagnosis, investigations and physical examination can be found in the 2020 edition of the MEA purple book – *ME/CFS/PVFS – An Exploration of the Key Clinical Issues.***

<https://meassociation.org.uk/product/clinical-and-research-guide/>

**Why is making an early and accurate diagnosis so important??**

\* To reduce the likelihood of ME/CFS taking a more prolonged and severe course.

\* To check for other conditions that can present with similar symptoms.

\* To prevent harmful approaches to management such as ‘working through fatigue’ and inappropriate exercise programmes.

\* To organise a comprehensive management plan involving activity and energy management; symptom relief; information and support relating to education, employment and sickness benefits.

**Taking a good clinical history**

The commonest age of onset is during the early 20s to mid 40s. However, all age groups, including children and adolescents, can be affected. ME/CFS affects all social classes and ethnicities.

ME/CFS is often triggered by an acute infection. This is followed by a ‘failure to recover’ with on-going flu like symptoms, feeling generally unwell and the development of characteristic ME/CFS symptoms. Other immune system stressors – e.g vaccinations – occasionally trigger ME/ CFS.

A gradual onset occurs in a minority with no clear precipitating event.

Adequate time should be allowed for taking a detailed history. This should include:

* past medical history
* medication use
* previous blood transfusion – to help exclude the possibility of hepatitis C infection
* social and family history
* recent overseas travel – ME/CFS can be triggered by tropical infections such as dengue
* psychological and mental well being
* the impact of ME/CFS on family life, education or employment

Where symptoms are atypical or ‘red flag’ in nature, occur in more elderly people, or are more pronounced than is normally found in ME/CFS, a more thorough clinical assessment is essential.

**Diagnostic criteria and characteristic core symptoms**

There are over 20 different diagnostic criteria for ME/CFS - the most recent being from the Institute of Medicine (IoM) in America. Most are designed for selecting homogenous groups of people for research purposes. They often have limitations for clinical practice diagnosis – where a more pragmatic approach is required.

There is no generally agreed diagnostic criteria for ME/CFS in a clinical setting and most criteria concentrate on the presence of core symptoms. Making a diagnosis therefore has to be based on a cluster of characteristic symptoms along with a careful consideration of other possible explanations.

A clinical diagnosis requires an inclusive approach – so it is important to be able to include people with a co-existing diagnosis of other conditions that can cause chronic fatigue in a way that many of definitions used for research purposes exclude.

**The key diagnostic feature is post-exertional malaise/symptom exacerbation** whereby symptoms are amplified by physical and/or mental exertion with a delayed impact – later the same day, the next day, or even later. This is then followed by a slow recovery period. The amount of activity that provokes symptom exacerbation can be very minimal.

**Core diagnostic symptoms:**

* **Cognitive dysfunction** involving problems with short-term working memory, concentration and attention span, information processing and retrieval, planning and organising thoughts, dysnomia and word-finding ability
* **Unrefreshing sleep pattern** may include hypersomnia (i.e excessive sleep requirements) in the early post-infection stage, fragmented sleep and myoclonic movements or restless legs syndrome later on. In more severe cases there may be a reversal of normal sleep rhythm (i.e being awake at night but sleeping during the day). NB: Excessive daytime sleepiness should raise the possibility of obstructive sleep apnoea - especially where there is snoring, early morning headaches and the person has a collar size above 16 inches (female) or 17 inches (male).
* **Autonomic nervous system dysfunction/dysautonomia** involving **orthostatic intolerance** (an inability to sustain physical or mental activity whilst standing) and in some cases **orthostatic hypotension** (a fall in blood pressure on standing resulting in dizziness or feeling faint) or **postural orthostatic tachycardia syndrome** (a significant rise in pulse rate on standing)..

**Pain** can affect muscles (myalgia), joints (arthralgia) and nerves (neuropathic) but is minimal or not present at all in a minority of people. Pain is often difficult to alleviate with simple analgesics and may be accompanied by sensory disturbances/paraesthesiae.

The above list of core symptoms is based on the 5 key symptoms – fatigue, post-exertional malaise/symptom exacerbation, cognitive dysfunction, orthostatic intolerance, unrefreshing sleep - in the IoM diagnostic criteria. Two major criticisms of the IoM criteria is that it requires symptoms to be present for at least 6 months and there very little emphasis is placed on the importance of considering the possibility of other causes of an ME/CFS like illness. Revised guidance from NICE on the diagnosis of ME/CFS will appear in the new guideline. This is due to be published in April 2021.

**Other symptoms may include:**

* **Poor temperature control** including increased sensitivity to hot and cold environments, sweating episodes, feeling feverish.
* **On-going flu like symptoms** including sore throats and tender glands without pathological enlargement.
* **Intolerance to alcohol, chemicals and medications** - especially psychotropic (antidepressant) drugs.
* **Headaches** of a new type or severity that may have a migrainous quality.
* **Sensory disturbances** including paraesthesiae (‘pins and needles’) and increased sensitivity to noise (hyperacusis) and bright light (photophobia).
* **Digestive disturbances** consistent with irritable bowel syndrome (i.e abdominal pain, bloating, change in bowel habit) may develop following the onset of ME/CFS and be exacerbated by certain foods (e.g wheat or dairy products).

Symptoms characteristically fluctuate in severity, throughout the day, day to day, and from week to week. The pattern of symptoms, along with severity, may change over time. So people will often describe a pattern of ‘good days’ and ‘bad days’.

Overall, there should a substantial (50% or more) and sustained reduction in both physical and cognitive/mental activity. This results in a substantial reduction in the capability to carry out pre-illness levels of occupational, educational, social or personal activity.

Where the diagnosis has been delayed the clinical presentation is likely to be more complex with a wider range of symptoms and symptom severity.

Exacerbations and relapses are commonly caused by infections, trauma and other stressors. This can include a pre-menstrual or menstrual exacerbation in some cases.

**People with severe ME/CFS** are often very sensitive to bright light, noise, movement, touch and smell. They may have substantial neurological impairments, including atypical seizures (fits), unwanted muscle activity/myoclonus and speech problems. Swallowing difficulties that may require nasogastric (tube) feeding.

**Physical examination**

A full clinical examination should include:

\* Checking for anaemia, thyroid, pathological lymphadenopathy and skin signs of systemic disease such as Addison’s disease

\* Pulse and blood pressure supine and standing

\* Checking for joint hypermobility in younger patients

\* Recording and monitoring weight in children and people with severe ME/CFS

NB: A study from the ME/CFS Biobank indicates that hand grip strength has the potential to be used as a clinical biomarker and a marker of disease severity (Nacul L *et al* 2018)

NB: People with ME/CFS show characteristic abnormalities which are consistent with post exertional malaise when they carry out a two day cardiopulmonary exercise test (CPET). This test has the potential to be used for both diagnosis and management (Keller BA *et al* 2014). CPET testing is not widely available in the UK for people with ME/CFS.

**Baseline investigations**

There is no diagnostic blood test for ME/ CFS. Baseline investigations are essential in order to check for common conditions that can cause chronic fatigue and should include:

\* Full blood count and differential

\* Serum ferritin

\* ESR and CRP (C-reactive protein)

\* Metabolic screen for calcium, phosphorous, urea and electrolytes, total protein, albumin and globulin, blood sugar and/or HbA1C

\* Coeliac disease screening test – IgA endomysial or tissue transglutaminase

\* Creatine kinase

* Random blood sugar and/or HbA1C

\* Serum creatinine

\* Liver function tests

\* Thyroid function tests

\* Urinalysis for protein, blood and glucose

The results should all be within normal limits. Where abnormalities occur, consideration must be given to other diagnostic explanations.

NB: Results from a study of blood samples collected by the ME/CFS Biobank indicate that the level of **creatine kinase** can be significantly reduced in people with severe ME/CFS and that this is a potential biomarker for severe ME/CFS (Nacul L et al, 2019).

A wide range of immune system abnormalities occur in ME/CFS, including changes in cytokine status and the presence of low levels of some autoantibodies. However, none of these abnormalities are sufficiently sensitive or specific to be used as diagnostic biomarkers.

**Further assessment and investigation**

**Indications:**

* Atypical symptoms (e.g joint pain accompanied by swelling)
* Red flag symptoms or signs (e.g weight loss, significant lymphadenopathy, fever, focal neurological signs, muscle wasting, generalised pruritis, dry eyes and mouth)
* Symptoms not normally associated with ME/CFS (e.g breathlessness or chest pain suggestive of cardiorespiratory disease)
* History, examination or baseline test results suggest other possible diagnostic explanations

**Examples:**

* Autoantibody screen – where a rheumatological or autoimmune condition is possible
* Schirmer’s test for dry eyes – possibility of Sjorgen’s Syndrome
* Screening for infectious diseases – giardia, hepatitis B/C, HIV, Lyme disease, Q fever, toxoplasmosis
* Synacthen test – where Addison’s disease is a possibility
* Serum hydroxyvitamin D – in housebound patients\*
* NASA 10 minute lean to test or tilt-table testing where there is significant autonomic system dysfunction
* Epworth sleepiness score on Pittsburg Sleep Quality Index where a primary sleep disorder is possible
* Polysomnography where sleep disturbance strongly suggests a primary sleep disorder such as sleep apnoea.

**Differential diagnosis**

Patient evidence and data collected by NHS referral services indicates that a significant number of people are being misdiagnosed as having ME/CFS. Of 260 people who attended the Newcastle ME/CFS referral service with a possible diagnosis of ME/CFS, 40% were found to have another explanation. 47% had another medical disorder, 20% a primary sleep disorder, 15% psychiatric/psychological illness and 4% cardiovascular disease (Newton JL et al, 2010). Thisis often due to a failure to carry out a proper clinical assessment and consider other possible explanations for an ME/CFS like illness.

Examples include

Addison’s disease

Coeliac disease

depression

fibromyalgia

haemochromatosis

hepatitis C

hypothyroidism

malignancy

multiple sclerosis

myasthenia gravis

primary biliary cirrhosis

primary sleep disorders such as sleep apnoea

rheumatic disease – eg Sjogren’s Syndrome

vitamin D deficiency

Although unlikely, it should be noted that the common conditions being checked for can sometimes co-exist with ME/CFS. So having hypothyroidism does not mean that the person could not have ME/CFS as well.

**TIMESCALE**

Most ME/CFS research criteria stipulate that a diagnosis should only be made after six months of symptoms. In clinical practice this should normally be regarded as the endpoint of the diagnostic process.

A working or interim diagnosis is better than no diagnosis at all and allows for active management to begin. A confirmatory diagnosis often needs to be pieced together through a series of consultations.

**Up to six weeks**: A working diagnosis of post-viral fatigue syndrome can be made where appropriate. Where a child has missed around four weeks of school, action must be taken to speed up the diagnostic process.

**At three months:** A provisional diagnosis of ME/CFS can often be made if symptoms persist and no other explanation is found. Diagnosis should normally have been confirmed in children and adolescents.

**By four months:** The provisional diagnosis should have normally been confirmed in adults. A management plan should now be in place.

Where there is continuing uncertainty about the diagnosis, or symptoms are severe, patients should be referred to a hospital-based ME/CFS referral service.

**Children and adolescents**

* ME/CFS has been reported in children as young as five. There appears to be a peak onset of symptoms around 13 to 15.
* ME/CFS can be misdiagnosed as a behaviour problem or school phobia.
* Children and adolescents may present differently to adults. Symptoms that are more common or prominent include stomach pain, nausea, headache and loss of appetite. There is growing evidence to indicate that hypermobility syndromes are more common in children and adolescents.
* ME/CFS is reported to be the commonest cause of long-term sickness absence from school.
* Children should be known to community paediatric services and under consultant care if they are unable to attend school on a regular basis.

**Specialist referral**

Where there is uncertainty about the diagnosis, or symptoms are severe, patients should be referred to a hospital-based ME/CFS service.

If there is not a suitable ME/CFS referral service nearby, the Countess of Mar has established through a House of Lords parliamentary question that people can be referred elsewhere to an NHS service/consultant of their choice:

<https://meassociation.org.uk/2014/07/can-mecfs-patients-choose-their-own-consultants-government-exploring-the-issue-28-july-2014/>

The MEA website has contact details of all the multidisciplinary hospital-based referral services for adults and children throughout the UK. While there are a considerable number of adult services in most parts of England there are very few NHS referral services in Northern Ireland, Scotland and Wales. Paediatric referral services are very limited throughout the UK. Website link:

<https://meassociation.org.uk/nhsspecialistservices/>

The MEA has an information leaflet covering Specialist Referrals in more detail.

**FURTHER INFORMATION**

* The MEA purple book - *ME/CFS/PVFS: An Exploration of the Key Clinical Issues* - summarises and references key information on research, clinical assessment and management.
* The MEA has leaflets covering all aspects of management: symptom relief, benefits, employment, etc.
* The ME Connect helpline provides information and support to people with ME/CFS. Contact details can be found on the MEA website: www.meassociation.org.uk
* The Chief Medical Officer’s Report on ME/CFS, NICE guideline on ME/CFS, Canadian diagnostic criteria, and Institute of Medicine diagnostic criteria can all be downloaded from the MEA website document archive (see About The MEA > Policies and Documents).

**REFERENCES:**

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**DISCLAIMER**

Drug and medical information contained in this leaflet is not intended to be a substitute for medical advice or treatment from your doctor. The ME Association recommends that you always consult your doctor or dentist about any specific problem. We also recommend that any medical information provided by The MEA is, where appropriate, shown to and discussed with your doctor or dentist.

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