Investigation of suspected chronic fatigue syndrome/myalgic encephalopathy

BACKGROUND Chronic fatigue is a frequently occurring problem in both the primary and specialist health services. The Department of Neurology at Haukeland University Hospital has established a standard assessment for patients referred with suspected CFS/ME. This study reports diagnoses and findings upon assessment, and considers the benefit of supplementary examinations.

MATERIAL AND METHOD Diagnoses and findings from examinations of 365 patients assessed for suspected CFS/ME are retrospectively reported.

RESULTS A total of 48 patients (13.2 %) were diagnosed with CFS/ME, while a further 18 patients (4.9 %) were diagnosed with post-infectious fatigue. Mental and behavioural disorders were diagnosed in 169 patients (46.3 %), and these represented by far the largest group. Serious, but unrecognised somatic illness was discovered in two patients, while changes of uncertain significance were identified by MRI and lumbar puncture in a few patients.

INTERPRETATION Fatigue is a frequently occurring symptom in the population. Thorough somatic and psychiatric investigation is necessary before referral to the specialist health services. Mental disorders and reactions to life crises are common and important differential diagnoses for CFS/ME. Long waiting times in the specialist health services may result in delayed diagnosis for these patients.

Jone Furlund Owe
jfow@helse-bergen.no
Department of Neurology
Haukeland University Hospital

Halvor Næss
Department of Neurology
Haukeland University Hospital
and
University of Bergen

Ivar Otto Gjerde
Department of Neurology
Haukeland University Hospital

Jørn Eilert Bødtker
Clinic of psychosomatic medicine
Haukeland University Hospital

Ole-Bjørn Tysnes
Department of Neurology
Haukeland University Hospital
and
University of Bergen

MAIN MESSAGE

Anxiety and depression disorders were frequent causes of the symptom complex in patients for whom chronic fatigue syndrome/myalgic encephalopathy (CFS/ME) was suspected

Somatic assessment in the primary health service was very good, but objective psychiatric evaluation of patients with suspected CFS/ME was inadequate

Self-reporting of fatigue by patients was poorly suited to distinguishing CFS/ME from other conditions associated with fatigue

The reported prevalence of CFS/ME is 0.2–3 % (7–9). In the period from 2008–12, 5 809 persons in Norway received the ICD-10 diagnosis G93.3 (10). This figure will include patients with CFS/ME, but it is not known whether all these fulfil the established criteria for this condition. The absence of biomarkers represents a challenge in terms of diagnosis, as does the need to exercise clinical discretion with regard to the significance of other explanations for the symptom complex. According to the Norwegian Directorate of Health guidelines (11), the diagnoses neurasthenia and burn-out will also be relevant for this patient group.

The core symptom of CFS/ME is persistent fatigue (> 6 months) that is unrelated to exertion. Rest does not help, and other conditions cannot explain the fatigue. Several sets of criteria for the condition are available (12).

The Norwegian Directorate of Health (11) recommends the Canadian criteria (13) or the Fukuda criteria (14). In 2015, the American Institute of Medicine published a report (15) in which they reviewed the criteria and scientific evidence base for the condition. They concluded by presenting new criteria, and the term Systemic Exertion Intolerance Disease (SEID) was proposed. These criteria have met with criticism (16) and are neither validated nor used in scientific publications.

On 1 February 2012, the Department of Neurology at Haukeland University Hospital established a standardised assessment for patients referred with suspected CFS/ME. In this study we summarise findings and diagnoses in the first 365 patients who were assessed. Our aim was to report the final diagnosis for these patients and to evaluate the benefit of comprehensive medical assessment.

Material and method

The referrals were considered by the neurologist responsible for the assessments. In cases where a diagnosis of CFS/ME could not apply, the referral was rejected. In the period 1 February 2012–4 July 2014, a total of 381 patients were assessed. Altogether 16 had previously been assessed for the same problem and are not included in the study. As a result, the study population consists of 365 patients assessed for CFS/ME.

The assessment was performed in the neurological day-care ward, but it was also possible to use inpatient wards. A medical history, clinical neurological examination, blood samples and a cerebrospinal fluid test were taken (e-box 1), and an EEG examination, measurement of orthostatic blood pressure, ECG and psychiatric evaluation were performed. MRI scan of the brain and spinal cord were also performed if this had not been undertaken previously. If an MRI scan of the brain alone had been performed, this was not repeated to cover the spinal cord if nothing pathological had been found in the brain.

Table 1 Diagnoses in all 365 patients studied, and in those classified as having chronic fatigue syndrome/myalgic encephalopathy (CFS/ME), postviral fatigue syndrome, or none of these diagnoses

	Total (n = 365)	CFS/ME (n = 48)	Postviral fatigue syndrome (n = 18)	Not CFS/ME/ G93.3 (n = 299)
Anxiety disorders (F40–47)	77	1	1	75
Mood [affective] disorders (F30–39)	64	1	2	61
Neurasthenia (F48)	54	0	0	54
Other F-diagnoses	20	0	0	20
Primary sleep disorders	44	0	0	44
Nutritional deficiency	42	2	1	39
Burn-out	22	0	0	22
Thyroid disorders	17	1	0	16
Fibromyalgia/chronic muscle pain	16	0	0	16
Borrelia infection	8	0	2	6
Headaches	8	1	0	7
Diabetes mellitus	5	0	0	5
Coeliac disease	3	0	1	2
Adrenal insufficiency	3	0	0	3[1]
Inflammation (chronic meningitis)	3	0	0	3
Acute cerebral venous sinus thrombosis	1	0	0	1
Chronic sinusitis	1	0	0	1
Polycystic ovary syndrome	1	0	0	1
Epilepsy	1	0	0	1
Irritable bowel syndrome	1	0	0	1
Atrial fibrillation	1	0	0	1
Total number of diagnoses	**392**	**6**	**7**	**379**
No specific diagnosis	47	0	0	47

[1] Two patients had previously diagnosed adrenal insufficiency

The patients had completed the forms for the Fatigue Severity Scale (FSS) (17) and the Hospital Anxiety and Depression Scale (HADS) in advance (18). The HADS form gives a score for anxiety and depression, with a threshold value of 8 of a maximum 21 points for anxiety and depression separately (19). With regard to the FSS result, a score of ≥ 5 is suggested as the threshold value for pathological tiredness (20). Further examinations were performed where indicated (for example sleep recording, assessment by a specialist in infectious diseases or by an endocrinologist).

Most of the patients were examined by the same doctor (JFO), and all were discussed in the pre-ward round. Psychiatric evaluation was conducted by the child and adolescent psychiatry outpatient clinic for patients in the age group 15–18 years. Those over 18 were assessed by a specialist in psychiatry or psychology at the clinic of psychosomatic medicine by means of a clinical interview, evaluation of previous documentation, M.I.N.I. Plus structured interview and the Montgomery-Åsberg Depression Rating Scale (MADRS).

The total estimated time spent per patient was eight hours. When appointments were scheduled, the patients were informed that the assessment might take up to five days. The assessment took place during this period, and patients were on leave of absence from work while awaiting tests, supplementary examinations and finally the pre-discharge interview.

The pre-discharge interview included a review of the investigations that had been conducted, and the diagnostic assessment and justifications. If necessary, the patients were referred for further follow-up by the somatic or psychiatric health service.

The Canadian criteria (13) for CFS/ME were used, and those who fulfilled the criteria received a diagnosis of G93.3 Chronic fatigue syndrome. Those who did not fulfil these criteria, but who were considered to have postviral fatigue with no other cause, received a diagnosis of G93.3 Postviral fatigue syndrome.

Diagnoses resulting from the assessments and findings of supplementary examinations were recorded.

The project was submitted to the Regional Research Ethics Committee which judged it to be a quality-assurance project not requiring an application for ethical approval (ref. 2014/560). The project was approved by the personal data Ombudsman at Haukeland University Hospital (ref. 2014/4249).

Results

Diagnoses

Of 365 patients referred with suspected CFS/ME, 48 (13.2 %) were found to fulfil the Canadian criteria for the condition and received a diagnosis of G93.3 Chronic fatigue syndrome. A further 18 patients (4.9 %) were not regarded as fulfilling the criteria, but these had postviral fatigue and received a diagnosis of G93.3 Postviral fatigue syndrome.

Diagnoses encompassed by ICD-10 Chapter V(F) (F00–F99 Mental and Behavioural Disorders) were considered to be the cause of the symptom complex in 169 of the patients (46.3 %). These diagnoses consisted mainly of F30–39 Mood [affective] disorders (17.5 %), F40–47 Neurotic, stress-related and somatoform disorders (21.1 %), and F48 Neurasthenia (14.8 %).

Table 1 shows the distribution of diagnoses in the group with CFS/ME, the group with postviral fatigue, and the remaining patients. Of the 48 patients diagnosed with CFS/ME, two also received diagnoses encompassed by ICD-10 Chapter V(F), but it was concluded that these fulfilled the criteria for CFS/ME. Two patients with postviral fatigue had previously had a confirmed diagnosis of Lyme neuroborreliosis.

Many patients had several diagnoses encompassed by ICD-10 Chapter V(F) (F00–F99). Of those who received these diagnoses, both new conditions and previous

Table 2 Age and gender distribution, in all patients and in patients with chronic fatigue syndrome/myalgic encephalopathy (CFS/ME), with postviral fatigue syndrome and with no CFS/ME or postviral fatigue syndrome

	Total (N = 365)	CFS/ME (n = 48)	Postviral fatigue syndrome (n = 18)	No CFS/ME/G93.3 (n = 299)
Average age (years) (range)	33.5 (15–70)	33.9 (16–55)	29.1 (15–48)	34.2 (15–70)
Number of women as a percentage (number)	80 (292)	81.3 (39)	77.8 (14)	79.9 (239)

diagnoses were relevant for the current symptom complex. Significant psychosocial stresses in some patients, for example in the form of bullying and abuse, were considered to be so extensive that they alone excluded a diagnosis of CFS/ME. For some of these, the problems were known to their GP, but an assessment was requested to establish whether the patient's symptom complex could nevertheless be ascribed to a mental disorder alone. Patients with recently diagnosed mental disorders requiring treatment were referred to the child and adolescent psychiatry outpatient clinic or district psychiatric centre, or to psychologists or psychiatrists in private practice.

The diagnosis Z73 burn-out was established in 22 patients (6.0 %). No specific diagnosis was made for 47 patients, who received symptom diagnoses such as R53 malaise and fatigue, or Z03.3 observation for suspected nervous system disorder. These were primarily patients with mild symptoms and no definitive somatic or mental illness, who did not fulfil the criteria for CFS/ME. Primary sleep disorders were found in 12.1 %, and these included circadian rhythm sleep disorders and obstructive sleep apnoea determined by Embletta recording. Nutritional deficiency was identified in 11.5 % of the patients, mainly iron deficiency and vitamin D deficiency.

Adrenal insufficiency was identified in one patient, and in another cerebral venous sinus thrombosis was detected by MRI scan taken during hospitalisation. These were the only confirmed findings of serious, non-recognised somatic illness in the study population.

Of the 365 patients studied, 80 % were women. The gender distribution was the same in those who received a diagnosis of CFS/ME and those with other diagnoses. Those who were diagnosed with postviral fatigue syndrome were somewhat younger than the rest of the study population (Table 2).

Self-reporting

The patients' self-reported symptoms are shown in Table 3. The FSS score was comparable between patients who received a diagnosis of CFS/ME and the others, while fewer patients with this diagnosis had a HADS core above the threshold value. Not all patients provided complete answers.

Supplementary examinations

A total of 285 patients had undergone MRI examination (Table 4), in 273 of whom there were normal findings. In one, cerebral venous sinus thrombosis was identified, and signal changes were found in 11, which were interpreted by a radiologist as being outside normal values.

One patient had a cortical lesion for which a low-grade glioma could not be ruled out, and one had signal changes that aroused suspicion of a demyelinating disease, although cerebrospinal fluid was normal. Both these patients had received a diagnosis of CFS/ME before the MRI examination was later performed at the outpatient clinic.

In two of the patients a possible pituitary adenoma was detected, but both had normal hormone status. Other secondary findings were non-specific signal changes, a syrinx with no clinical consequences and a case of post-traumatic degenerative changes.

Cerebrospinal fluid was examined in 314 of 365 patients (86.0 %). For the remainder this was either contraindicated, the patient did not want the examination, or the lumbar puncture was unsuccessful. Altogether 15 patients had an elevated number of bands in the cerebrospinal fluid, comprising 4–8 serum- and non-serum-like bands. None of these received a diagnosis of CFS/ME.

Inflammatory markers in the cerebrospinal fluid were found in five patients, with pleocytosis and/or detection of more than ten non-serum-like oligoclonal bands. MRI of the brain and spinal cord were normal in all five. Two had had neuroborreliosis and received a diagnosis of postviral fatigue syndrome. The remaining three were given the diagnosis G03.1 Chronic meningitis.

Table 3 Self-reported fatigue (Fatigue Severity Scale, FSS) and anxiety/depression (Hospital Anxiety and Depression scale, HADS) in patients with chronic fatigue syndrome/myalgic encephalopathy (CFS/ME), with postviral fatigue syndrome, and with no CFS/ME or postviral fatigue syndrome. HADS-A=anxiety score HADS-D=depression score. Not all patients provided complete answers

	FSS score			HADS-A score			HADS-D score		
		Above threshold value			Above threshold value			Above threshold value	
	Average (range)	Number	(%)	Average (range)	Number	(%)	Average (range)	Number	(%)
CFS/ME	6.3 (1.3–7.0)	40	(97.6)	5.0 (0–17)	7	(17.1)	5.0 (0–13)	10	(24,4)
Postviral fatigue syndrome	6.0 (5.0–7.0)	15	(100)	6.2 (0–16)	5	(35.7)	5.5 (0–13)	5	(35,7)
No CFS/ME/G93.3	6.1 (1.6–7.0)	207	(88.5)	7.1 (0–20)	98	(42.1)	6.9 (0–21)	103	(44,4)
All	6.1 (1.3–7.0)	262	(90.3)	6.8 (0–20)	110	(38.2)	6.6 (0–21)	118	(41,1)

Table 4 Result of supplementary studies in all patients, and in patients with chronic fatigue syndrome/myalgic encephalopathy (CFS/ME), with postviral fatigue syndrome and with no CFS/ME or postviral fatigue syndrome

		Total (N = 365)	CFS/ME (n = 48)	Postviral fatigue syndrome (n = 18)	No CFS/ME/ G93.3 (n = 299)
MRI brain/spinal cord	Normal	273	42	17	214
	Secondary findings	11	3	0	8
	Pathological	1	0	0	1
	Not performed	80	3	1	76
Cerebrospinal fluid	Normal	294	45	15	234
	Secondary findings	15	1	0	15
	Pathological	5	0	2	3
	Not performed	51	2	1	48
EEG	Normal	342	44	18	280
	Secondary findings	17	3	0	14
	Pathological	0	0	0	0
	Not performed	6	1	0	5
Orthostatic blood pressure and ECG	Normal	280	35	16	229
	Secondary findings	4	1	0	3
	Pathological	0	0	0	0
	Not performed	81	12	2	67

Repeated lumbar punctures were performed with cytology testing, immunophenotyping and testing for angiotensin-converting enzyme (ACE), a marker for sarcoidosis, in cerebrospinal fluid. The findings were stable, with no signs of malignancy or neurosarcoidosis. Repeated MRI examinations gave no grounds for suspicion of inflammatory disease. Altogether 14 patients experienced post-lumbar puncture headache which required the insertion of an epidural blood patch.

Standard EEG examination was performed in 359 patients (98.6 %). There were no pathological findings of clinical significance. Four patients experienced a fall in blood pressure during measurement of orthostatic blood pressure. One of these was diagnosed with CFS/ME.

Discussion

Using a standardised assessment, we studied 365 patients referred with suspected CFS/ME. Of these, 13.2 % were diagnosed based on the Canadian criteria. A further 4.9 % received a diagnosis of postviral fatigue syndrome, but did not fulfil the criteria for CFS/ME.

Most of the diagnoses were encompassed by ICD-10 Chapter V(F), of which anxiety and depression disorders constituted the majority. This confirms that mental disorders are highly important differential diagnoses with regard to symptoms of fatigue and lack of energy, as well as additional symptoms in the form of pain, impaired memory and concentration, and other symptoms that are included in the symptom complex surrounding CFS/ME.

In this study, evaluation by a specialist in psychiatry or psychology was an integral part of the assessment, and included a clinical interview and use of recognised forms. This has ensured a uniform assessment. Only two of 48 patients with a final diagnosis of CFS/ME were additionally diagnosed with a mental condition. This is somewhat in contrast to studies that have shown anxiety and depression to be common in patients with CFS/ME (21, 22).

According to the Canadian criteria, primary psychiatric conditions are exclusion diagnoses for CFS/ME, but anxiety and depression disorders may be regarded as comorbid conditions. Less psychopathology is found in patients who fulfil the Canadian criteria than in those who fulfil the Fukuda criteria (23). The final assessment as to whether the patient primarily has an anxiety and depression disorder, or whether this is secondary to a condition of persistent fatigue, will be based on a total assessment of the medical history and examination. Discretion is a factor in these assessments, since existing sets of criteria do not draw an unambiguous distinction between CFS/ME and cases in which the fatigue is secondary to mental illness.

There was no overlap between fibromyalgia and CFS/ME either – none of the 16 patients diagnosed with fibromyalgia received the latter diagnosis. Fibromyalgia has many features in common with CFS/ME (24), and it can be difficult to distinguish between the conditions. In this study, the diagnosis of fibromyalgia was made by a rheumatologist, either in this or an earlier assessment. In the fibromyalgia patients, persistent pain was clearly a precursor to fatigue, and we considered that the symptom complex could be explained on this basis. However, it is evident that some diagnostic uncertainty exists between CFS/ME and fibromyalgia, as is also the case for other overlapping conditions, for example irritable bowel syndrome (22, 25).

With few exceptions, the patients were referred from the primary healthcare service and had not previously been assessed specifically for CFS/ME in the specialist health services. We endeavoured to ensure that the assessment would be a low-threshold service for primary healthcare. Nevertheless, many patients were rejected when the diagnosis of CFS/ME was excluded, based on the information in the referral. The number of rejected referrals is not recorded, but this selection indicates that the proportion of referred patients who fulfil the criteria for CFS/ME is considerably lower than 13.2 %, as reported here.

As a consequence of capacity limitations in the radiological department, many patients underwent MRI examination in the outpatient clinic following assessment. From a neurological standpoint, this examination will have been conducted mainly to exclude demyelinating disease. MRI of the brain according to the multiple sclerosis protocol is, in our opinion, sufficient. Since MRI examination following the hospital assessment leads to uncertainty when discussing the diagnosis, we now request that the referring doctor arranges for the examination to be performed in advance.

Pathological cerebrospinal fluid was found in five patients. Altogether 14 patients experienced post-lumbar puncture headache requiring an epidural blood patch. Pathological cerebrospinal fluid resulted in further

investigation in three patients, with repeated MRI examinations and lumbar punctures. No specific diagnosis was made for these patients. Lumbar puncture is now performed only when clearly indicated, for example when MRI findings may indicate demyelinating disease, and not routinely.

Orthostatic intolerance is known to occur in cases of CFS/ME (26), and patients with postural orthostatic tachycardia are considered a clinical subgroup of these patients (27, 28). Orthostatic intolerance is also suggested as one of two supplementary SEID criteria (15). Only four of our patients experienced a fall in blood pressure. There was no difference between the patients with CFS/ME and the other patients.

In an examination of 365 patients, only one was found to have an underlying somatic condition (adrenal insufficiency) that had not been recognised and that could explain their fatigue. Cerebral venous sinus thrombosis was identified in one patient – but this could not explain the symptoms of persistent fatigue for which the patient was being assessed, and it was interpreted as a coincidence. Two patients are being monitored for possible somatic illness after findings of MR lesions that may indicate inflammation or low-grade glioma. This indicates that patients with suspected CFS/ME are thoroughly investigated for somatic illnesses in the primary health service.

Self-reporting forms for degree of fatigue showed little difference between those who were diagnosed with CFS/ME and those who received other diagnoses. We consider that the FSS form is unsuited for distinguishing CFS/ME from other conditions that involve fatigue. However, patients with the diagnosis scored above the threshold value on the HADS form less frequently than others, and this was the case for anxiety as well as depression. In our view, the HADS form may constitute a useful tool in differential diagnostic assessment of suspected CFS/ME.

Duration of symptoms was not recorded in this study. Most patients had had symptoms for several years before they attended for assessment. It is therefore essential that patients are assessed both somatically and psychiatrically in the primary health service before referral to the specialist health services. It is especially important to thoroughly assess psychosocial conditions in patients who present with this type of symptom complex. Anxiety and depression are serious conditions that are amenable to treatment, and long waiting times in the specialist health services may be very unfavourable for these patients if they go untreated.

It may also be called into question whether assessment of CFS/ME should take place in a neurological department, or whether other departments would be more appropriate. The diagnosis is found in the neurological chapter of ICD-10 (G93.3), but there is little by way of evidence from assessments that points unequivocally towards neurological disease. What is most important in our opinion is that the patients are examined systematically – it is of less importance which department performs the assessment. Following a standard assessment, with time, resources and availability of professionals from different specialties, the clinical assessment of suspected CFS/ME could be conducted with good precision in the course of a few days of elective hospitalisation.

In our opinion, for many the assessment must be conducted in the primary health service, based on the national guidelines from the Norwegian Directorate of Health (11). A detailed patient history, blood sample analysis and MRI examination of the brain and spinal cord are indicated. The assessment must also include specific evaluation of mental disorders, in particular anxiety and depression disorders.

In the absence of biomarkers for the condition, in the majority of cases assessment and diagnosis will need to be aimed at identifiable causes of fatigue, both somatic and mental, and findings of these will consequently explain the symptoms, and therefore exclude the diagnosis of CFS/ME. Given a structured assessment in the primary health service, our assumption is that the need for assessment in the specialist health services will be reduced and can be reserved for patients for whom the diagnosis is uncertain.

Conclusion

Fatigue is a common symptom in the population. Thorough investigation of somatic and mental illness in patients with pronounced, persistent fatigue is necessary before referral by the primary health service to the specialist health services. Somatic assessment in the primary health service captures most somatic causes, whereas mental disorders as a cause of fatigue are probably underdiagnosed. Mental disorders are frequent and important differential diagnoses in the assessment of CFS/ME.

Jone Furlund Owe (born 1975)
specialist in neurology with a PhD degree in myasthenia gravis. He is a senior consultant with responsibility for assessment of chronic fatigue syndrome/myalgic encephalopathy.
The author has completed the ICMJE form and reports no conflicts of interest.

Halvor Næss (born 1957)
specialist in neurology with a PhD degree in stroke. He is a senior consultant and professor.
The author has completed the ICMJE form and reports no conflicts of interest.

Ivar Otto Gjerde (born 1947)
specialist in neurology and senior consultant.
The author has completed the ICMJE form and reports no conflicts of interest.

Jørn Eilert Bødtker (born 1961)
specialist in psychiatry with long experience of assessment of fatigue-related conditions.
The author has completed the ICMJE form and reports the following conflicts of interest: he has received lecture fees from Novartis.

Ole-Bjørn Tysnes (born 1956)
specialist in neurology, professor and head of department.
The author has completed the ICMJE form and reports no conflicts of interest.

References

1. Loge JH, Ekeberg O, Kaasa S. Fatigue in the general Norwegian population: normative data and associations. J Psychosom Res 1998; 45: 53–65.
2. Kluger BM, Krupp LB, Enoka RM. Fatigue and fatigability in neurologic illnesses: proposal for a unified taxonomy. Neurology 2013; 80: 409–16.
3. Naess H, Lunde L, Brogger J. The triad of pain, fatigue and depression in ischemic stroke patients: the Bergen Stroke Study. Cerebrovasc Dis 2012; 33: 461–5.
4. Strober LB. Fatigue in multiple sclerosis: a look at the role of poor sleep. Front Neurol 2015; 6: 21.
5. Bower JE. Cancer-related fatigue – mechanisms, risk factors, and treatments. Nat Rev Clin Oncol 2014; 11: 597–609.
6. Dupond JL. Fatigue in patients with rheumatic diseases. Joint Bone Spine 2011; 78: 156–60.
7. Jason LA, Richman JA, Rademaker AW et al. A community-based study of chronic fatigue syndrome. Arch Intern Med 1999; 159: 2129–37.
8. Mulrow CD, Ramirez G, Cornell JE et al. Defining and managing chronic fatigue syndrome. Evid Rep Technol Assess (Summ) 2001; nr. 42: 1–4.
9. Nacul LC, Lacerda EM, Pheby D et al. Prevalence of myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) in three regions of England: a repeated cross-sectional study in primary care. BMC Med 2011; 9: 91.
10. Bakken IJ, Tveito K, Gunnes N et al. Two age peaks in the incidence of chronic fatigue syndrome/myalgic encephalomyelitis: a population-based registry study from Norway 2008–2012. BMC Med 2014; 12: 167.
11. Nasjonal veileder. Pasienter med CFS/ME: Utredning, diagnostikk, behandling, rehabilitering, pleie og omsorg. 2015. https://helsedirektoratet.no/retningslinjer/nasjonal-veileder-pasienter-med-cfsme-utredning-diagnostikk-behandling-pleie-og-omsorg (11.1.2016).
12. Fønhus MS, Larun L, Brurberg KG. Diagnosekriterier for kronisk utmattelsessyndrom. Notat – 2011. www.kunnskapssenteret.no (15.2.2015).
13. Carruthers BM, Jain AK, De Meirleir KL et al. Myalgic Encephalomyelitis/ Chronic Fatigue Syndrome: Clinical Working Case Definition, Diagnostic and Treatment Protocols. Journal of Chronic Fatigue Syndrome 2003; 11: 7–36. http://med.stanford.edu/content/dam/sm/chronicfatigue/documents/overview/CanadianCriteriaCFS2003.pdf (11.1.2016).

>>>

14. Fukuda K, Straus SE, Hickie I et al. The chronic fatigue syndrome: a comprehensive approach to its definition and study. Ann Intern Med 1994; 121: 953–9.
15. Beyond myalgic encephalomyelitis/chronic fatigue syndrome: redefining an illness Committee on the Diagnostic Criteria for Myalgic Encephalomyelitis/ Chronic Fatigue Syndrome. Washington D.C.: Board on the Health of Select Populations, Institute of Medicine, National Academies Press, 2015.
16. Twisk FN. A critical analysis of the proposal of the Institute of Medicine to replace myalgic encephalomyelitis and chronic fatigue syndrome by a new diagnostic entity called systemic exertion intolerance disease. Curr Med Res Opin 2015; 31: 1333–47.
17. Krupp LB, LaRocca NG, Muir-Nash J et al. The fatigue severity scale. Application to patients with multiple sclerosis and systemic lupus erythematosus. Arch Neurol 1989; 46: 1121–3.
18. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand 1983; 67: 361–70.
19. Bjelland I, Dahl AA, Haug TT et al. The validity of the Hospital Anxiety and Depression Scale. An updated literature review. J Psychosom Res 2002; 52: 69–77.
20. Lerdal A, Wahl A, Rustøen T et al. Fatigue in the general population: a translation and test of the psychometric properties of the Norwegian version of the fatigue severity scale. Scand J Public Health 2005; 33: 123–30.
21. Bould H, Collin SM, Lewis G et al. Depression in paediatric chronic fatigue syndrome. Arch Dis Child 2013; 98: 425–8.
22. Janssens KA, Zijlema WL, Joustra ML et al. Mood and Anxiety Disorders in Chronic Fatigue Syndrome, Fibromyalgia, and Irritable Bowel Syndrome: Results From the LifeLines Cohort Study. Psychosom Med 2015; 77: 449–57.
23. Jason LA, Torres-Harding SR, Jurgens A et al. Comparing the Fukuda et al.Criteria and the Canadian Case Definition for Chronic Fatigue Syndrome. J Chronic Fatigue Syndr 2004; 12: 37–52.
24. Lukkahatai N, Walitt B, Espina A et al. Understanding the association of fatigue with other symptoms of fibromyalgia: Development of a cluster model. Arthritis Care Res (Hoboken) 2015. E-publisert 27.5.
25. Clauw DJ. Perspectives on fatigue from the study of chronic fatigue syndrome and related conditions. PM R 2010; 2: 414–30.
26. Wyller VB, Fagermoen E, Sulheim D et al. Orthostatic responses in adolescent chronic fatigue syndrome: contributions from expectancies as well as gravity. Biopsychosoc Med 2014; 8: 22.
27. Nijs J, Ickmans K. Postural orthostatic tachycardia syndrome as a clinically important subgroup of chronic fatigue syndrome: further evidence for central nervous system dysfunctioning. J Intern Med 2013; 273: 498–500.
28. Reynolds GK, Lewis DP, Richardson AM et al. Comorbidity of postural orthostatic tachycardia syndrome and chronic fatigue syndrome in an Australian cohort. J Intern Med 2014; 275: 409–17.

Received 17 February 2015, first revision submitted 3 July 2015, accepted 10 January 2016. Editor: Sigurd Høye.