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13. september 2013

Vedrørende diagnosticering af Myalgisk encephalomyelitis – ME

ME Foreningen anbefaler de internationale konsensuskriterier (ICC) til diagnosticering af ME. Udredning af ME foregår ved dels at vurdere om patienten opfylder ICC diagnose-kriterierne, og dels ved at udelukke en lang række andre sygdomme.

ICC kriterierne og vejledning til udredning af patienter fremgår af International Consensus Primer for Medical Practitioners som kan downloades fra www.me-foreningen.dk

Imidlertid anbefaler det danske sundhedssystem stadig de ældre diagnosekriterier NICE guidelines til ME/CFS. Disse er en anelse bredere og kan omfatte patienter, der ikke har ME.

Det er under alle omstændigheder vigtigt med en meget grundig udredning, da ME Foreningen alt for tit oplever fejldiagnosticerede patienter.

Som støtte for udredningen kan nedenstående vejledning være til stor hjælp, idet der oplyses om differentialdiagnoser og henvises til mulige relevante analyser fra Statens Serum Institut.

Vedlagte vejledning er udarbejdet af neurolog Finn E. Somnier, M.D., D. Sc. (Med.).

Det skal understreges, at patienter IKKE selv kan henvende sig til Statens Serum Institut og Finn E. Somnier vedrørende denne vejledning. Alle patienthenvendelser skal ske gennem egen praktiserende læge. Man kan som patient medbringe denne vejledning til sin læge, der kan hjælpe med at udpege og få foretaget relevante analyser og laboratorietests fra vejledningen for at komme frem til en sikker diagnose.

ME Foreningen, 2013

Diagnosing chronic fatigue syndrome (CFS)

Alias Myalgic encephalomyelitis (ME), fibromyalgia

There is no test for chronic fatigue syndrome (CFS), but there are clear guidelines to help doctors diagnose it.

National Institute for Health and Care Excellence **(NICE) guidelines** (clinical guidelines CG53 issued August 2007) **for diagnosing CFS**
In addition to the presence of fatigue, **all of the following criteria must apply**: ➢ it is new or had a clear starting point (it has not been a lifelong problem) ➢ it is persistent and/or recurrent ➢ it is unexplained by other conditions ➢ it substantially reduces the amount of activity someone can do ➢ it feels worse after physical activity
The patient should also have **one or more of these symptoms**: • difficulty sleeping, or insomnia • muscle or joint pain without inflammation • headaches • painful lymph nodes that are not enlarged • sore throat • poor mental function, such as difficulty thinking • symptoms getting worse after physical or mental exertion • feeling unwell or having flu-like symptoms • dizziness or nausea • heart palpitations, without heart disease
For more information, read the NICE guidelines on CFS; and/or National Guideline Clearinghouse: Chronic fatigue syndrome/myalgic encephalomyelitis. A primer for clinical practitioners

This diagnosis should be confirmed by a clinician after other conditions have been ruled out, and the above symptoms have persisted for at least four months in an adult and three months in a child or young person.

However, it can take a long time for the condition to be diagnosed, **as other conditions that cause similar symptoms need to be ruled out first.**

Not exhaustive listing of differential diagnoses

Internal medicine

Perform blood and urine tests & scans to rule out other conditions, such as anaemia, liver, kidney problems or an underactive thyroid gland
http://www.ssi.dk/Diagnostik/DiagnostiskHaandbog/400-499/480.aspx

Rheumatologic disorders

1. **Polymyositis and more**
   http://www.ssi.dk/Diagnostik/DiagnostiskHaandbog/400-499/499.aspx
   Analysis: Myositis analysis package (SSI req. number 499)
   Contents
   - EJ (Glycyl-tRNA synthetase) antibody IgG
   - Jo-1 (Histidin--tRNA-ligase) antibody IgG
   - Mi 2 (Chromodomain-helicase-DNA binding protein 4) antibody IgG
   - Ku antibody IgG
   - OJ (Isoleucyl-tRNA synthetase) antibody IgG
   - PL-12 antibody IgG
   - PL-7 antibody IgG
   - PM-Scl75 (Exosome complex exonuclease RRP45) antibody IgG
   - PM-Scl100 (Exosome component 10) antibody IgG
   - Ro-52 antibody IgG
   - SRP antibody IgG

   http://www.ssi.dk/Diagnostik/DiagnostiskHaandbog/400-499/411.aspx
   ANA Screening (please see website for details)
2. **Rheumatoid arthritis**
   http://www.ssi.dk/Diagnostik/DiagnostiskHaandbog/4300-4399/4344.aspx
   Contents
   - Reuma factor (IgM) (SSI req. number 401)
   - Reuma factor (IgA) (SSI req. number 402)
   - CCP: Antbody (IgG) (SSI req. number 442)
   - hsCRP analysis (SSI req. number 576)

Neurological or autonomic disorders

1. **Neuromuscular: Myasthenia gravis – Lambert-Eaton myasthenic syndrome**
   http://www.ssi.dk/Diagnostik/DiagnostiskHaandbog/400-499/487.aspx
   Analysis: Myasthenia gravis package (SSI req. number 487)
   Contents
   - **Anti-AChR (adult) (SSI req. number 446)**
   - Anti-Titin (SSI req. number 449)
   - Anti-MuSK (SSI req. number 447)
   - Anti-Ca-channel (P/Q-type) – (SSI req. number 712)
2. **Autoimmune synaptic encephalitis**
   - http://www.ssi.dk/Diagnostik/DiagnostiskHaandbog/400-499/480.aspx

   Analysis: Autoimmune Synaptic Encephalitis Package (SSI req. number 3453)
   Contents
   - **Anti-NMDAR (NR1, SSI req. number 4352)**
   - Anti-AMPAR1 (SSI req. number 4354)
   - Anti-AMPAR2 (SSI req. number 4356)
   - Anti-LGI1 (SSI req. number 4314)
   - Anti-CASPR2 (SSI req. number 4311)
   - Anti-Gaba(B)R1 (SSI req. number 4355)
   - Anti-GAD (SSI req. number)

- http://www.ssi.dk/Diagnostik/DiagnostiskHaandbog/4300-4399/~/media/Indhold/DK%20-%20dansk/Diagnostik/DiagnostiskHaandbog/Autoimmun%20encephalitis.ashx

3. **Post-streptococcal neurology**
   http://www.ssi.dk/Diagnostik/DiagnostiskHaandbog/4300-4399/4309.aspx
   Analysis: Post-streptococcal neurological syndrome, package (SSI req. number 4309)
   Contents (cannot be required seperately)
   - **CamKII activity**
   - Anti-Lyso-GM1
   - Anti-D1 (anti-Dopamine receptor D1)
   - **Anti-D2 (anti-Dopamine receptor D2)**
   - Anti-beta-Tubulin
4. **Hashimoto's encephalitis and autoimmune thyroiditis**
   http://www.ssi.dk/Diagnostik/DiagnostiskHaandbog/400-499/480.aspx
   Analysis: Thyroiditis package (SSI req. number 480)
   Contents
   - Anti-TPO (SSI req. number 468)
   - Anti-TG (SSI req. number 478)
   - Anti-TSH (SSI req. number 404)
5. **Paraneoplastic neurological syndromes**
   http://www.ssi.dk/Diagnostik/DiagnostiskHaandbog/400-499/497.aspx
   Analysis: Paraneoplastic neurological syndrome, package (SSI req. number 497)
   Contents
   - Anti-Hu (SSI req. number 432)
   - Anti-Yo (SSI req. number 435)
   - Anti-Ri (SSI req. number 497)
   - Anti-Amphiphysin1
   - Anti-CV2 (CRMP5) (SSI req. number 497)
   - Anti-Ta (Ma2)
6. **Autoimmune agrypnia (insomnia) –** test serum for anti-Gamma-Aminobutyric Acid B Receptor 1 (SSI req. number 3454 (package) or separately as 4355)
7. **Dysautonomia (please see review pages 4 to 7) –** Anti-AChR (alpha3 type)

Neuropsychiatric

1. **Pervasive Refusal Syndrome (PRS)** – proposed new name **Pervasive Arousal Withdrawal Syndrome (PAWS)**
   Other references:
   a) Oslo Universitetssykehus: Pervasive Refusal Syndrome
   b) Tine Jaspers T, Hanssen GMJ, van der Valk JA, ,Hanekom, JH, van Well GTJ, Schieveld JNM. **Pervasive refusal syndrome as part of the refusal–withdrawal–regression spectrum: critical review of the literature illustrated by a case report.** Eur Child Adolesc Psychiatry. 2009 November; 18(11): 645–651
   c) Wright D, Beverley. **Pervasive Refusal Syndrome.** Clinical Child Psychology and Psychiatry 2012; 17 (2): 221
   d) Kenneth P, Nunn KP, Lask B, Owen I. **Pervasive refusal syndrome (PRS) 21 years on: a re-conceptualisation and a renaming.** European Child & Adolescent Psychiatry 2013 June;

Overview: **Dysautonomia - Wikipedia**

Please also see: **Paraneoplastic autonomic polyneuropathy**

Dysautonomia (or **autonomic dysfunction**) is any disease or malfunction of the autonomic nervous system (ANS). The autonomic nervous system controls a number of functions in the body, such as heart rate, blood pressure, digestive tract peristalsis, and sweating, amongst others. Dysfunction of the ANS can involve any of these functions.

A number of conditions are forms of dysautonomia: postural orthostatic tachycardia syndrome (POTS), inappropriate sinus tachycardia (IST), vasovagal syncope, pure autonomic failure, neurocardiogenic syncope (NCS), neurally mediated hypotension (NMH), orthostatic hypotension, orthostatic hypertension, autonomic instability, and a number of lesser-known disorders such as cerebral salt-wasting syndrome. Dysautonomia may occur as the result of other diseases, such as diabetes mellitus, multiple system atrophy (Shy-Drager syndrome), Guillain-Barré syndrome, and Ehlers-Danlos syndrome, along with a number of other conditions that may affect the nervous system

TABLE 1: Predominantly Pediatric Autonomic Disorders

Aetiology	Classification	Disorders	Gene
Developmental disorders	Hereditary sensory and autonomic disorders	FD (HSAN type III) CIPA (HSAN type IV) Congenital sensory neuropathy (HSAN type II)	IKBKAP *NTRK1* Unknown
	Allgrove syndrome		*AAAS*
	Cardiorespiratory dysregulation disorders	CCHS Long-QT syndrome	*PHOX2B* 6 genes (*KCNQ1, KVLQT1, HERG*, *SCN5A*, *KCNE1*, *MiRP1*)
	Chromosomal disorders	Prader-Willi syndrome	? gene/Ch15q11-q13
		Fragile X	*FMR1*/Ch X
		Rett syndrome	*MECP2*/Ch X
Biochemical errors	Myopathies	Mitochondrial myopathies: Leber hereditary optic neuropathy; X-linked kinky-hair disease; Leigh syndrome; Kerns-Sayre syndrome; Myoneurogastrointestinal disorder with encephalopathy	Mitochondrial DNA point mutations
		Nemaline myopathy	*TPM3*, *NEB*
		Central core disease	Ryanodine receptor gene
	Neurotransmitter deficiencies	Dopamine β-hydroxylase deficiency	*DBH*
		Menkes	*MNK*
	Storage disorders	Fabry disease	*GLA*
	Metabolic/endocrine disorders	Diabetes	
		Addison disease/Cushing disease	
		Thyroid disorders	
Unknown	**Genetic, autoimmune including post-infectious and paraneoplastic**	Autism	
		Cyclic vomiting syndrome (CVS)	
		Functional abdominal pain	
		Chronic fatigue syndrome (CFS)	
		Pandysautonomia (autonomic polyneuropathy)	
		Post-infectious autoimmune encephalitis	
		Postural orthostatic tachycardia syndrome (POTS)	
		Sudden infant death syndrome	
		Late-onset alveolar hypoventilation with obesity and hypothalamic dysfunction	
	Prematurity		

Please see Tables 2, 3, 4 and 5 for details.

TABLE 2: Autoimmune disorders with autonomic features			
Peripheral		**Central**	
Pandysautonomia	Anti-AChR of alpha-3 type	Autoimmune synaptic encephalitis	Synaptic autoantibodies
Polyradiculitis (Guillain-Barré-like)	Ganglioside autoantibodies, anti-Heparan, anti-MAG	Paraneoplastic neurologic disorders	Paraneoplastic autoantibodies
		Post-infectious CNS (e.g., tics, myokymia, chorea, fasciculations and more) – *post-streptococcal*	CamKII activity, anti-lyso-GM1, anti-D1, anti-D2, anti-Tubulin, anti-Keratin
		ADEM	Anti-MOG and MRI
Differential diagnoses			
CNS vasculitis	Various MRI techniques, ANCA screening etc., brain biopsy		
Aluminium encephalopathy	Serum aluminium		

TABLE 3: Functions of the Autonomic Nervous System		
Organ	**Sympathetic Nervous System**	**Parasympathetic Nervous System**
Eye		
Pupil	Dilatation	Constriction
Ciliary muscle	Relax (far vision)	Constrict (near vision)
Lacrimal gland	Slight secretion	Secretion
Salivary glands	Slight secretion	Secretion
Heart	Increased rate	Decreased rate
	Positive inotropism	Negative inotropism
Lungs	Bronchodilation	Bronchodilation
Gastrointestinal	Decreased motility	Increased motility
Kidney	Decreased output	None
Bladder	Relax detrusor	Contract detrusor
	Contract sphincter	Relax sphincter
Penis	Ejaculation	Erection
Sweat glands	Secretion	Palmar sweating
Blood vessels		
Arterioles	Constriction	None
Muscles		
Arterioles	Constriction or dilatation	None
Metabolism	Glycogenolysis	None

TABLE 4: The extensive circuitry of which ranges from the forebrain to the brainstem: **Anatomy and Function**		
Anatomic Area	**General Function**	**Clinical Manifestations**
Insular and medial prefrontal cortices	High-order autonomic control: input from gastric mechanoreceptors, arterial chemoreceptors, baroreceptors	Cardiac arrhythmia
Extended amygdala	Autonomic expression of emotional states: integrates autonomic and motor responses	Viscero-sensory phenomena (e.g., unilateral hyperhidrosis)
		Vomiting (left temporal focus)
		Sexual arousal
Hypothalamus	Homeostasis: initiates and coordinates biological rhythms, autonomic, neuroendocrine, and behavioural responses	Hypothermia or hyperthermia
		Poor stress response (autonomic storm)
		Insomnia
Midbrain	Coordinates autonomic, pain-controlling, and motor mechanisms for stress-related, aggressive, and reproductive behaviours	Hypertension or hypotension, arrhythmias
		Intractable vomiting and dysmotility
		Hypoventilation
		Urinary retention
Pons	Relays viscero-sensory information to forebrain	
Nucleus of the tractus solitarius	Relays viscero-sensory information from vagus and glossopharyngeal nerves to other CAN regions	
Medulla	Cardiovascular and respiratory control via premotor autonomic and respiratory neurons controlling input to spinal, respiratory, and preganglionic motor neurons	Sleep-disordered breathing (e.g., apnoea, alveolar hypoventilation)

TABLE 5:

Functional Organization of Symptoms Associated With Autonomic Nervous System Disorders

System	Dysfunction	Symptom
Vasomotor/cardiovascular	Hypertension	Headache
	Hypotension	Dizziness, light-headedness
	Arrhythmia	Loss of consciousness/syncope
	Vascular irritability	Acrocyanosis, cold hands and feet, blotching
Gastrointestinal	Oropharyngeal dysmotility	Feeding problems (poor suck, drooling, aspiration pneumonia)
	Oesophageal dysmotility	Dysphagia (difficulty swallowing)
	Gastroesophageal reflux	Nausea
	Bowel dysmotility	Recurrent vomiting
		Bloating
		Profound constipation or diarrhoea
Ophthalmologic	Alacrima	Dry eye
	Nonreactive/sluggish pupils	Dark/light intolerance
	Anisocoria	Severe myopia
	Ptosis	Strabismus
Respiratory	Alveolar hypoventilation	Cyanosis with sleep
	Apnoea	Breath-holding spells
	Insensitivity to hypoxia	Syncope at high altitudes/plane travel
	Insensitivity to hypercarbia	
Sudomotor	Altered sweating	Hypohidrosis or hyperhidrosis
	Thermoregulatory abnormalities	Decreased basal body temperature
		Excessively dry skin
		Unexplained high fevers
Neurologic	Altered perception of pain	Sensory defensiveness
		Decreased response to injury, injections, and dental procedures
		Self-mutilation
	Sleep/wake disturbance	Insomnia
Urologic	Delayed bladder emptying	Nocturnal enuresis (>5 years of age)
Psychological	Altered affect	Poor socialization skills
	Unusual emotional responses	Increased anxiety
	Poor executive planning	Poor school performance
	Learning disability	Emotional lability
	Attention problems	Tics/phobias

Selected references to CFS (none of these data have been reproduced by other independent groups)

Tanaka S, Kuratsune H, Hidaka Y, Hakariya Y, Tatsumi KI, Takano T, Kanakura Y, Amino N. **Autoantibodies against muscarinic cholinergic receptor in chronic fatigue syndrome.** Int J Mol Med. 2003 Aug; 12(2): 225-30.

Source
Department of Laboratory Medicine, Osaka University Graduate School of Medicine (D2), Suita-shi, Osaka 565-0871, Japan. tanaka@labo.med.osaka-u.ac.jp

Abstract
The disturbance of the central nervous system and immunological abnormalities has been suggested in patients with chronic fatigue syndrome (CFS). We focused on immunological abnormalities against neurotransmitter receptors in CFS. Using a sensitive radioligand assay, we examined serum autoantibodies to recombinant human muscarinic cholinergic receptor 1 (CHRM1), mu-opioid receptor (OPRM1), 5-hydroxytryptamine receptor 1A (HTR1A), and dopamine receptor D2 (DRD2) in patients with CFS (n=60) and results were compared with those in patients with autoimmune disease (n=33) and in healthy controls (n=30).

The mean anti-CHRM1 antibody index was significantly higher in patients with CFS ($p<0.0001$) and autoimmune disease ($p<0.05$) than that in healthy controls, and positive reaction was found in 53.3% of patients with CFS. The patients with positive autoantibodies to CHRM1 had a significantly higher mean score (1.81) of 'feeling of muscle weakness' than negative patients (1.18) among CFS patients ($p<0.01$). Higher scores on 'painful node', 'forgetfulness', and 'difficulty thinking' were also found in CFS patients with anti-CHRM1 antibodies but did not reach statistical significance. ***[Comment by Finn Somnier: Increased titre of anti-AChR (adult type) in combination with muscular weakness is diagnostic of myasthenia gravis].***

Anti-OPRM1 antibodies, anti-HTR1A antibodies, and anti-DRD2 antibodies were found in 15.2, 1.7, and 5.0 % of patients with CFS, respectively. ***[Comment by Finn Somnier: A finding of anti-Dopamine receptor 2 is a marker of post-streptococcal neurology and may also play a role in this disorder].***

Anti-nuclear antibodies were found in 56.7% (34/60) of patients with CFS, but anti-nuclear antibody titters did not correlate with the activities of the above four autoantibodies.

In conclusion, autoantibodies to CHRM1 were detected in a large number of CFS patients and were related to CFS symptoms. Our findings suggested that subgroups of CFS are associated with autoimmune abnormalities of CHRM1. ***[Comment by Finn Somnier: If this is the case, then a diagnosis of CFS may probably be inappropriate and vice versa, a diagnosis of myasthenia gravis should be considered].***

Vernon SD, Reeves WC.
Evaluation of autoantibodies to common and neuronal cell antigens in Chronic Fatigue Syndrome. J Autoimmune Dis. 2005 May 25; 2: 5.

Source

Division of Viral and Rickettsial Diseases, National Center for Infectious Diseases, Centers for Disease Control and Prevention, Atlanta, Georgia 30333, USA. svernon@cdc.gov

Abstract

People with chronic fatigue syndrome (CFS) suffer from multiple symptoms including fatigue, impaired memory and concentration, unrefreshing sleep and musculoskeletal pain. The exact causes of CFS are not known, but the symptom complex resembles that of several diseases that affect the immune system and autoantibodies may provide clues to the various etiologies of CFS. We used ELISA, immunoblot and commercially available assays to test serum from subjects enrolled in a physician-based surveillance study conducted in Atlanta, Georgia and a population-based study in Wichita, Kansas for a number of common autoantibodies and antibodies to neuron specific antigens. Subsets of those with CFS had higher rates of antibodies to microtubule-associated protein 2 (MAP2) ($p = 0.03$) and ssDNA ($p = 0.04$). There was no evidence of higher rates for several common nuclear and cellular antigens in people with CFS. Autoantibodies to specific host cell antigens may be a useful approach for identifying subsets of people with CFS, identify biomarkers, and provide clues to CFS etiologies.

Oscar-Danilo Ortega-Hernandez [a] and Yehuda Shoenfeld [a, b, c]
Infection, Vaccination, and Autoantibodies in Chronic Fatigue Syndrome, Cause or Coincidence?
Contemporary Challenges in Autoimmunity: Ann NY Acad Sci 2009; 1173: 600–609

Source

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[c] Incumbent of the *Laura Schwarz-Kip Chair for Autoimmunity, Tel-Aviv University, Tel-Aviv, Israel*

Abstract

Chronic fatigue syndrome (CFS) is a heterogeneous syndrome of unknown aetiology and physiopathology. CFS patients complain about disabling fatigue, depression, difficulty with memory, and concomitant skeletal and muscular pain. Interestingly enough, there is certain overlap between CFS symptoms, autoimmune rheumatic disease, and infectious diseases. Certain neuroendocrine-immune abnormalities have also been described, and autoantibodies commonly described in some autoimmune diseases have been found in CFS patients as well. An increasing number of autoantibodies, mainly directed against other nuclear cell components, have been illustrated. Likewise, an association between some infectious agents, antibody production, and later CFS onset has been reported. Similarly, vaccination is depicted as playing an important role in CFS onset. Recently, a case report pointed toward a causal association between silicone breast

linkage, hepatitis B virus vaccination, and CFS onset in a previous healthy woman. Such findings suggest that there is a likely deregulation of the immune system influenced by specific agents (infections, vaccination, and products, such as silicone). Evidence suggests that CFS is a complex disease in which several risk factors might interact to cause its full expression. Thus, although different alterations have been found in CFS patients, undoubtedly the main feature is central nervous system involvement with immunological alterations. Therefore, a new term *neuro*-psycho-*immunology* must be quoted. New studies based on this concept are needed in order to investigate syndromes, such as CFS, in which immunological alterations are thought to be associated with concomitant psychological and health disturbances.

Extracts from this publication:

TABLE 1. Infectious Agents Associated with Chronic Fatigue Syndrome Onset

Microorganism	**Possible mechanism of Microorganism association**	**References**
HPV-B19	Postinfection	25–27
HHV-6	Reactivation	28–30
Dengue	Postinfection	31
EBV	Postinfection	33, 37
RRV	Postinfection	32
HBV	Postinfection	15, 34
HVC	Postinfection	37
Enterovirus	Postinfection	37
Retrovirus	Postinfection	37
VZV	Reactivation	36
HSV	Reactivation	37
Coxiella burnetii (Q fever)	Postinfection	32, 33

HPV-B19, human parvovirus B19; HHV-6, human herpes virus-6; EBV, Epstein–Barr virus; RRV, Ross River virus;HBV, hepatitis B virus; HCV, hepatitisCvirus; VZV, varicella zoster virus; HSV, herpes simplex virus

TABLE 2. Vaccination and Chronic Fatigue Syndrome Onset

Vaccine	Risk	Protection	Vaccination recommended	References
Rubella	Yes	No	Yes	44
Q fever	Yes	No	Yes	45
HBV	Yes	No	Yes	45–47
Meningococcal vaccine	No	No	Yes	50
Poliovirus	No	No	Yes	52
Staphylococcus toxoid	No	Yes	Yes	53
Influenza virus	No	No	Yes	54, 55

Comment by Finn E. Somnier: none of these associations have been confiormed by the Board on Population Health and Public Health Practice

TABLE 3. Antibodies Associated with Chronic Fatigue Syndrome			
Antibody		Reported	References
Antibodies in AIDs	Anti-dsDNA	No	17, 19
	Anti-Sm	No	19
	Anti-RNP	No	19
	Anti-SS-A/Ro	No	19
	Anti-SS-B/LA	No	19, 24
	Anti-Scl-70	No	19, 24
	ANA	Yes	57
Nuclear components	Laminin B1	Yes	17, 56
	68/48-kDa nuclear protein[a]	Yes	58
	p80-coilin nuclear protein[b]	Yes	59
Phospholipid antibodies	Antiphosphatidylinositol[c]	Yes	21, 61, 62
Antibodies to CNS components	Serotonin	Yes	20, 21, 61
	ACTH	Yes	22
	CHMR1 **(Comment by Finn E. Somnier: not a CNS feature)**	Yes	23
	Microtubule-associated protein 2 (MAP2)	Yes	19
Antibodies to diverse microorganisms	Gram-negative enterobacteria[d]	Yes	65
	Coxiella burnetii (Q fever)[e]	Yes	66
Abbreviations: AIDs, autoimmune rheumatic diseases; dsDNA, double-stranded DNA; ACTH, adrenocorticotrophic hormone; ANA, anti-nuclear antibodies; CHMR1, muscarin cholinergic receptor 1; MAP2, microtubule associated protein 2; RNP, ribonucleoprotein			
A Clinically associated with hypersomnia and cognition complaints; **B** Found in Japanese patients, mainly the IgG 1 and 2 subclasses; **C** Antiphosphatidylinositol IgM and IgG antibodies; **D** Both IgM and IgG antibodies against enterobacteria were reported; **E** Both IgM and IgG antibodies against Coxiella burnetii were reported			
Comment by Finn E. Somnier: Please note that in many cases such findings **are supporting differential diagnoses rather than a diagnosis of CFS per se**			