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From neurasthenia to post-exertional disease: evolution of the diagnostic criteria for chronic fatigue syndrome/myalgic encephalomyelitis

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Summary

We present the evolution of terminology and diagnostic criteria for chronic fatigue syndrome/myalgic encephalomyelitis.

This syndrome is a complex and controversial entity, of unknown etiology, which appeared in the medical literature in 1988, although since the 19th century clinical pictures of idiopathic chronic fatigue were identified with different names, from neurasthenia, epidemic neuromyasthenia and benign myalgic encephalomyelitis to the current proposal for exercise intolerance disease (post-exertion). All of them refer to a chronic state of generalized fatigue of an unknown nature, with limitations to physical and mental effort, accompanied by a set of symptoms that compromise various organic systems.

The International Classification of Diseases (ICD-10) includes this syndrome in the section on neurological disorders (G93.3), although no anatomopathological findings have yet been found that clarify it.

Multiple organic alterations have been documented, but a common biology has not been established to clarify the mechanisms underlying this disease. It is stated as a neuroimmunoendocrine dysfunction, with an exclusively clinical diagnosis and by exclusion.

Various authors have proposed including chronic fatigue syndrome/myalgic encephalomyelitis within central sensitivity syndromes, alluding to central sensitization as the common pathophysiological substrate for this syndrome and others.

The role of the family doctor is key in the disease, for the detection of those patients who present fatigue of an unknown nature that continues continuously or intermittently for more than 6 months, in order to make an early diagnosis and establish a plan of action against a chronic disease with high levels of morbidity in the physical and mental sphere.

Target

To carry out a bibliographic review of the terminology and diagnostic criteria of chronic fatigue syndrome/myalgic encephalomyelitis, in order to conceptually clarify the disease, as a diagnostic tool for Primary Care physicians.

Keywords: Neurasthenia, Epidemic neuromyasthenia, Benign myalgic encephalomyelitis, Chronic fatigue syndrome, Exercise intolerance disease (post-exertional), Central sensitivity syndromes

Introduction

The terms of fatigue, asthenia or tiredness are synonymous from the clinical point of view. Fatigue is a symptom that is perceived and referred, therefore, it is subjective. It can be expressed in various ways: acutely it constitutes a homeostatic protection mechanism and chronically (lasting at least 6 months) it constitutes a "permanent disease state" associated with both medical and psychological illness, whether known or idiopathic .

In the International Classification of Diseases (ICD-10), fatigue or asthenia is included in chapter XVIII (R00-R99) under the heading: "Symptoms, signs and abnormal clinical and laboratory findings, not classified elsewhere", figure with code R53 [1](#) .

Fatigue definitions are very loose. It is a polysemic, multidimensional and variable term that ranges from "feeling of exhaustion of mind and body that follows an effort, associated with a desire to rest and a refusal or inability to make any other effort" [2](#) to "subjective sensation of lack of energy or physical or mental exhaustion, weakness, during or after usual tasks, not necessarily associated with physical activity, leading to a decreased ability to lead a normal life or having to make an effort to carry out usual activities» [3](#) .

Academically, "peripheral" (muscular) fatigue can be differentiated from "central" (neural) fatigue, although they are closely related. The "peripheral" can be defined as a lower force development than expected as a result of exhaustive muscular work; Strength losses due to damage or factors not directly related to muscle activation are excluded [4](#). While "central" fatigue is a sustained feeling of tiredness that is not directly related to physical activity, although it disproportionately worsens it and does not improve with rest; patients feel tired first thing in the morning, it is accompanied by an inability to carry out any activity, it presents with complaints of physical and cognitive weakness and appears as the integration of emotions, volition, cognition and motility [2](#) . Within this concept, "mental" fatigue represents the inability to complete mental tasks that require self-motivation, in the absence of demonstrable cognitive deficit and motor [weakness](#) .

When fatigue is chronic and of unknown origin associated with other symptoms, it has received various names throughout history: neurasthenia, epidemic neuromyasthenia, atypical poliomyelitis, Akureyri disease, Iceland disease, Da Costa or irritable heart syndrome, Royal Free Hospital disease, vegetative neuritis, combat exhaustion syndrome, benign myalgic encephalomyelitis, postviral fatigue syndrome, myalgic encephalopathy, raphe nuclei encephalopathy, chronic mononucleosis syndrome, chronic fatigue syndrome, neuroimmunoendocrine dysfunction syndrome, syndrome of the Gulf War and exercise intolerance disease, among others [6](#) . Whether all these tables, or some of them, are the same or partly overlap is something that remains to be clarified.

On the other hand, chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME) is a syndrome with defined criteria, with multiple alterations in various systems, as corresponds to a disease with multisystemic repercussions, but a pathophysiogenic mechanism has not yet been determined. nor a clear pathological substrate, either at the organic, cellular or molecular level.

The estimated prevalence of fatigue in Primary Care varies between 6% and 32%, 5-15% suffer from

chronic fatigue (>6 months) and 0.5-4.4% suffer from CFS [7](#) . Other authors indicate a prevalence of chronic fatigue in the United States of 11.1% and in the United Kingdom of 10.4% , [8](#) a figure that reaches 33% in [Japan](#) . In contrast, for ME/CFS, the ranges vary depending on the methodology (between 0.0052% and 6.40%) [10](#) . This wide variation found in epidemiological studies responds to the complexity of both the fatigue symptom and the controversy over the diagnostic criteria used for ME/CFS.

In this work we carry out a review of the evolution of the terminology used (1869-2015) and the evolution of the diagnostic criteria that have led to the 3 terms that coexist today in the medical literature as the most accepted: CFS, ME and exercise intolerance disease.

Developing

Neurasthenia

American physicians George Beard (1839-1883) and Edwin van Deusen (1828-1910) developed the concept of neurasthenia in their 1869 publications [11](#) , [12](#) .

For Beard it was a functional disease of the brain, which consisted of exhaustion caused by excessive work or stress of a preferably mental type (high demand on the nervous system). This was presented above all in the North American man of liberal profession.

As predisposing causes for presenting this condition, dyspepsia, cardiovascular diseases were postulated—because they lead to poor nutrition of the brain— or sexual excesses, in addition to a certain hereditary predisposition and the influence of the climate. According to the dominant symptoms, he distinguished various clinical forms: cerebral, spinal, gastrointestinal, cardiac, and genital or sexual. Both authors agreed on the causes, but, in terms of symptoms, Van Deusen included malaise, irritability, depression and melancholy.

It currently appears in ICD-10 in chapter V (F00-F99) «Mental and behavioral disorders», as a neurotic disorder with code (F48.0) [13](#) .

There are considerable cultural variations in the presentation of this disorder, although 2 main types can be identified, although there is a great deal of overlap between them. In one, the main complaint is increased fatigue after mental effort, related to decreased work performance or daily tasks; instead, the other emphasizes physical weakness and exhaustion after minimal exertion, accompanied by symptoms such as muscle aches and an inability to relax. Both types are accompanied by dizziness, tension headache, irritability, anhedonia, sleep disturbances, depression, and anxiety.

epidemic neuromyasthenia

The EN referred to a syndrome whose symptoms included fatigue, depression, pain, muscle weakness, headache and paresthesia, among others. Patients present involvement of the central and autonomic nervous system as well as the reticuloendothelial system. Abnormal muscle fatigability is the essential feature, pointing to possible mitochondrial damage [14](#) .

This picture was initially described in epidemic outbreaks, hence its name. Between 1934 and 1977, around 30 epidemic outbreaks were reported, mainly affecting young and middle-aged women [15](#) . These outbreaks were attributed to various infectious agents, such as the Epstein-Barr virus, the most frequent that is related to debilitating fatigue, but also others such as cytomegalovirus, *Toxoplasma gondii* , *Giardia lamblia* , *Coxsackie* , hepatitis A, *Mycoplasma pneumoniae* or herpes zoster , although the most frequent was unknown origin [16](#) .

benign myalgic encephalomyelitis

During the decade from 1945 to 1955, a series of epidemic outbreaks of unknown origin that mimicked characteristics of poliomyelitis were reported throughout the world. As a result of all this, *The Lancet* (1956) published under the title «A new clinical entity?» an analysis of the characteristics of these epidemic outbreaks of unknown origin, differentiating them from other processes such as poliomyelitis, epidemic myalgia, glandular fever, other forms of epidemic encephalitis and also from hysteria. The editorial proposed and argued for all these processes the term benign MS. The authorship of said editorial and the concept were finally attributed to the British epidemiologist Donald Acheson (1926-2010).

These epidemics or sporadic cases present the following common characteristics: symptoms and signs of cerebrospinal damage, muscle pain, with paresis and cramps, emotional disorders during convalescence, normal cerebrospinal fluid, compromise of the reticuloendothelial system in some cases, chronic course with evolution relatively benign and deterioration in the most severe cases [17](#) .

In 1957, Wallis, in his doctoral thesis: "An investigation into an unusual disease seen in epidemic and sporadic form in a general practice in Cumberland in 1955 and subsequent years", also referred to the term encephalomyelitis of unknown origin ("an obscure disease that mimics poliomyelitis"), to refer to this syndrome [18](#) .

At length, Lindan described benign MS in the following terms: "Onset resembles that of poliomyelitis, with headaches, tiredness, stiff neck and sore throat, accompanied by pain in the limbs and back." , and possibly paresthesia and paralysis. In contrast to polio, however, the fever is not very high, the temperature rarely exceeds 37.7°C and can persist for long periods. The clinical picture is dominated by severe muscle pain, initially accompanied by spasms and exaggerated tendon reflexes. These pains are not transient, often persisting long after the local signs have subsided, and may be accompanied by increased tenderness, but no loss of muscle mass develops at any time. An additional hallmark of the disease is the appearance of behavioral changes, such as emotional lability, irritability, and depression. Alterations of the cranial nerves (diplopia and nystagmus), facial weakness, deafness or, conversely, in some cases, hyperacusis are also common. A high proportion of cases show involvement of the reticuloendothelial system, with enlargement of the cervical lymph nodes, particularly those of the posterior triangle, and in some patients, hepatitis and splenomegaly»A high proportion of cases show involvement of the reticuloendothelial system, with enlargement of the cervical lymph nodes, particularly those of the posterior triangle, and in some patients, hepatitis and splenomegaly»A high proportion of cases show involvement of the reticuloendothelial system, with enlargement of the cervical lymph nodes, particularly those of the posterior triangle, and in some patients, hepatitis and splenomegaly»[19](#) .

This MS nomenclature was well received and replaced other processes with similar characteristics such as epidemic neuromyasthenia (referred to above), Royal Free Hospital disease, Akureyri disease or atypical poliomyelitis.

The Royal Society of Medicine in its 1978 symposium addressed some of the problems that this denomination presented. The first is that 50% of cases progress without muscle pain and the second refers to the term "benign": it is correct in that it does not lead to the death of patients, but it does not reflect the serious disability that the disease causes in patients affected. The term "benign" has been falling into disuse in usual medical communication, although the classifications continue to include it. In the aforementioned symposium it was concluded that it is an entity with multiple causes. In this sense, it was pointed out that a persistent viral infection (coxsackie, chickenpox, influenza, Epstein-Barr, etc.) and damage to the immune system appeared as the main causes. Other etiologies were also

postulated, such as alterations in the metabolism of the nervous system and muscle tissue, involvement of the raphe nuclei, and others, and psychosomatic nature was ruled out.[20](#) .

The World Health Organization, in 1967, classified MS within the diseases of the area of the central nervous system, with code 323 (ICD-8) [21](#) . Subsequently, in 1975 it appeared within the encephalitis of non-specific cause with the code 323.9 (ICD-9) [22](#) and in 1992 (ICD-10), within the epigraph of other diseases of the nervous system such as postviral fatigue syndrome/benign myalgic encephalomyelitis (G93.3) [23](#) . Along these same lines, it appears in the latest revision of the ICD-11 with the code 8E49 [24](#) .

Melvin Ramsay (1901-1990), from the Department of Infectious Diseases at the Royal Free Hospital in London, described the features of MS, referring to the disease in the following terms: «a disconcerting syndrome with tragic consequences» [25](#) . In 2011, the international consensus criteria were published, which establish the non-specific concept of “post-exertional neuroimmune exhaustion” as the cardinal symptom, together with other neurological, gastrointestinal, genitourinary, and immunological symptoms and in energy production mechanisms [26](#) ([Table 1](#)).

Table 1

Comparative analysis between chronic fatigue syndrome, myalgic encephalomyelitis and effort intolerance disease

Criteria	Chronic Fatigue Syndrome (CFS) Fukuda, 1994	Myalgic encephalomyelitis (ME) Carruthers, 2011	Exercise intolerance disease (SEID) Wright, 2015
Greater	Chronic fatigue (6 months or more): idiopathic, definite onset, does not go away with rest, substantially reduces activities	Marked and rapid fatigue, physical and cognitive, in response to exertion, which may be minimal Post-exertional discomfort with aggravation of symptoms, and slow recovery, greater than 24 h	Chronic fatigue (6 months or more): idiopathic, definite onset, does not go away with rest, substantially reduces activities Post-exertional malaise with aggravation of symptoms, with a slow recovery, greater than 24 h
Minors	unrefreshing sleep Post-exertional malaise lasting more than 24 hours Altered concentration or recent memory Odynophagia Painful cervical or axillary lymphadenopathy Myalgias Polyarthralgias, without signs of swelling or redness Headache of a new type, pattern or severity (characteristics different from the usual ones)	<p><i>1. Neurological symptoms (4 categories)</i></p> neurocognitive disorders Pain sleep disturbances Neurosensory alterations <p><i>2. Immunological, gastrointestinal and genitourinary symptoms (5 categories)</i></p> Flu-like symptoms Susceptibility to viral infections, with prolonged recovery periods Gastrointestinal: nausea, abdominal pain, bloating, irritable bowel syndrome Genitourinary: Urinary urgency or frequency, nocturia Sensitivity to food, medications, odors, or chemicals <p><i>3. Alterations in energy metabolism (4 categories)</i></p> Cardiovascular: orthostatic intolerance, neural hypotension, postural orthostatic tachycardia, palpitations without cardiac arrhythmias, dizziness, lightheadedness Respiratory: choking, breathing difficulties, respiratory muscle fatigue Loss of thermostatic stability Intolerance to temperature changes	Neurocognitive disorders Orthostatic intolerance
Diagnosis	Major criteria and at least 4 of 8 minor criteria symptoms	Typical: major criterion + Other criteria (3 categories + 3 categories + 1 category) Atypical: major criterion. Other criteria, variable No need to wait 6 months	Major criterion and at least one of the 2 minor criteria
	Need to wait 6 months		Need to wait 6 months

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Chronic Fatigue Syndrome

In 1988, the term CFS first appeared in the medical literature, proposed by the Division of Viral Diseases (Centers Control Disease, USA). It refers to a clinical picture of chronic fatigue (more than 6

months of evolution), with easy physical and cognitive fatigue, of an unknown nature, associated with other symptoms such as low-grade fever, lymphadenopathy, sore throat, etc., which replaces at the end of chronic Epstein-Barr syndrome [27](#) .

This nomenclature of CFS did not replace that of ME, but both terms were equated in the first world symposium on this disease held in 1990 at the University of Cambridge, where the current name of CFS/ME was sanctioned. On the other hand, regarding the nature of this disease, one of the conclusions of the meeting was clear, establishing that it is an organic disease of still unknown origin [28](#) .

At this time, other diagnostic criteria were also published, such as those of *Oxford* [29](#) that establish a subtype of CFS: *post-infectious fatigue syndrome* .

Shortly after, in 1994, the Centers Control Disease (USA) established the so-called international consensus diagnostic criteria, specifically for CFS, and which continue to be the most widely used today, both from a diagnostic and research point of view .

These focus on the presence of a major criterion: idiopathic chronic fatigue that does not go away with rest, that substantially reduces activity and that also requires compliance with 4 minor criteria from a panel of 8 [30](#) ([Table 1](#)).

In 2003, the International Group for the Study of Chronic Fatigue Syndrome highlighted the contradictions in the 1994 diagnostic criteria in some recommendations [31](#) . In this same year, a group of experts led by the Canadian Carruthers (1933-2017) established the Canadian Consensus Criteria for ME/CFS [32](#) .

It should be noted that the group led by Carruthers, a few years later, in 2011, alluded to the need to clearly separate ME from CFS, proposed the international consensus criteria for ME (mentioned above) and indicated that patients evaluated with the Fukuda (1994) CFS criteria should be reassessed with these new criteria.

Numerous studies provide data on the validity of the Fukuda criteria, the most frequently used today for the diagnosis of this condition, but none measure their reproducibility: up to 20 criteria have been recorded in a systematic review [33](#) .

In our country in 2008, the Consensus Document on CFS [34](#) appeared , and a review of the scientific evidence (2017) sponsored by the Carlos III Health Institute and the Agència de Qualitat i Avaluació Sanitàries de Catalunya [35](#) , which highlight the need to better understand the syndrome.

exercise intolerance disease

In 2015, the National Academy of Sciences of the United States of America (Institute of Medicine) proposed the name systemic exertion intolerance disease (SEID) for these idiopathic chronic fatigue states . As major criteria, they advocated the presence of idiopathic chronic fatigue with a substantial reduction in social and work activities together with post-exertional illness and unrefreshing sleep, and as minor criteria, orthostatic intolerance and neurocognitive alterations.

A comparative analysis of the international consensus criteria for CFS, ME and this new proposal (SEID) reveals the different diagnostic phenotypes ([Table 1](#)), as well as the lack of consensus that, together with the absence of an animal model for basic research, make it difficult to define this entity.

In this context of nomenclatures and proposals for diagnostic criteria , [33](#) there are authors who propose including these syndromes, together with others, under the concept of central sensitivity syndromes (CSS), alluding to central sensitization as a pathophysiological mechanism common to all of them . [37](#) , [38](#) . Instead, others use the terminology of *chronic overlapping pain conditions* [39](#) .

All these diseases share a higher female prevalence, pain, tiredness, sleep problems, generalized hyperalgesia, and the absence of clear signs of peripheral injury [40](#) .

Conclusions

Idiopathic chronic fatigue states associated with neurological, immunological, and emotional symptoms have received multiple names throughout history, such as neurasthenia, epidemic neuromyasthenia, ME, CFS, and the current SEID proposal.

From a practical point of view, the family doctor should suspect the presence of this syndrome in a patient who reports fatigue lasting more than 6 months, either continuously or intermittently. All this with an analysis and exploration that do not reflect any alteration that could explain the state of weakness and incapacity that the patient refers and that makes it difficult or even impossible for him to maintain normal activity.

The complexity of this picture requires the collaboration of other colleagues to establish the diagnosis. To date there are no objective criteria that help in the diagnosis or monitoring of this disease, so it is necessary to investigate to clarify its aetiopathogenic mechanisms.

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What is known about the subject / What this study contributes

- The estimated prevalence of fatigue in Primary Care varies between 6% and 32%, 5-15% suffer from chronic fatigue (>6 months) and 0.5-4.4% have CFS.
- The definition of ME/CFS requires compliance with specific clinical criteria that have been modified throughout history.
- A knowledge of the disease helps to improve the quality of life of these chronic patients, reduces the time to diagnosis, therefore generates satisfaction between patient and doctor, and requires fewer health resources.

Conflict of interests

The authors declare that they have no conflict of interest.

Footnotes

^{Annex} Additional material to this article can be consulted in its electronic version available at [doi:10.1016/j.aprim.2019.04.004](https://doi.org/10.1016/j.aprim.2019.04.004) .

Annex A. Supplementary Material

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