Case Report

Varied Presentation of Myalgic Encephalomyelitis/ Chronic Fatigue Syndrome and the Needs for Classification and Clinician Education: A Case Series

Eva Martín-Martínez, MBBS[1]; and Mercedes Martín-Martínez, PhD[2]

[1]National Health Service, Manises Hospital, Valencia, Spain; and [2]Instituto de Química Médica (CSIC), Madrid, Spain

ABSTRACT

Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) is a complex, heterogeneous and serious disease. In this article, we analyze the cases of 3 patients with ME/CFS. Due to the disbeliefs, misconceptions, and stigmas that are attached to ME/CFS, patient diagnosis is made after years of disease progression. Over this period, physicians tried to determine the etiology of the disease, taking into account its onset and symptoms. The suspected conditions correlated with possible subgroups that researchers speculate may exist in ME/CFS. Therefore, a registry of well-selected data on clinical history could help to cluster patients into more homogenous groups, and could be beneficial for research. (*Clin Ther*. 2019;41:619–624) © 2019 Published by Elsevier Inc.

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BACKGROUND

Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) is a complex, chronic, and commonly debilitating disease of unknown etiology and with no effective treatment. Symptoms can vary from patient to patient and include physical and mental debilitating fatigue, not restful sleep, orthostatic intolerance, and exertion intolerance. The World Health Organization considers ME/CFS a serious neurologic disease, and it is codified in the *International Statistical Classification of Diseases and Related Health Problems*, 10th *Revision* as G 93.3.

The estimated worldwide prevalence of ME/CFS is between 0.2% and 1%, with a peak prevalence between the ages of 20 and 40 years and a higher prevalence in women.[1,2] This disease impairs quality of life. It is estimated that over 80% of patients with ME/CFS are unable to work, which causes a substantial economic impact. Besides a lack of productivity, there is also a direct cost due to the economic burden associated with health services, tests, and treatments.

Despite being a severe disease, there is an important gap in the diagnosis and treatment of ME/CFS in health care systems worldwide, motivated mainly by a lack of up-to-date medical training. Due to this lack of training, many times health care providers do not suspect that a patient has ME/CSF and might refer him or her to a mental health practitioner. The diagnosis may be reached only after a patient eventually meets a heath care provider who knows the pathology of ME/CSF. Even in these cases, there may be no specialist center that can properly care for these patients.

Currently, there are no approved diagnostic tests, physical examination signs, or biological markers specific for this disease; thus, the diagnostic criteria are based on consensus after other pathologies that present with similar symptoms have been ruled out. Moreover, the substantial variability of the disease from patient to patient and a lack of knowledge of the exact pathogenesis hinder clear evidence that might guide clinical practice, treatment, or research.[3] These facts have also led researchers to approach the disease from different fields and with diverse

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hypotheses as to its source: the immune system, the CNS, the endocrine system, mitochondria, genetics, epigenetics, microbiota, the neuroendocrine system, and/or infection.

The research on ME/CFS has generated controversy regarding not only its etiopathogenesis but also possible treatments. At present, there is no cure for ME/CFS, and treatment is focused in symptom relief. Rituximab, a monoclonal antibody, has shown promising results in initial trials, with significant improvement in some patients.[4,5] However, preliminary data from a Phase III, double-blind clinical study indicate negative results. Nonetheless, this drug might be of utility in a subset of patients.[6]

Researchers are gathering evidence that different pathogenic mechanisms could be involved in ME/CFS, which would explain the clinical heterogeneity. Some investigators have pointed to the existence of 3 possible subgroups[7]: autoimmune profile, trigger by infection, and a third one of unknown causes. The classification of patients into subgroups would facilitate research.[8–10] However, the heterogeneity of patients with ME/CSF also interferes in studies, at 2 levels: (1) it might hinder the understanding of the molecular basis of the disease; and (2) treatments will be effective only if they target the effects of the disease, and treatments that act in intermediate or initial steps will be discarded.[11]

In addition, research on ME/CFS presents another challenge: how to obtain patient samples. As there is neither a medical specialty nor clinical department that assumes the diagnosis and monitoring of these patients, researchers have to search through advocacy groups and social networks. The lack of a clinical unit that specializes in ME/CFS usually leads to a delay in diagnosis, which is quite often reached only after years of progression.

In the search for the underlying cause of the pathology, it would be a priority to analyze and classify patients to create more homogeneous subgroups. To this end, it is of interest to analyse disease onset, as at the onset the pathogenic mechanism is the only responsible for the symptoms, and the compensatory mechanisms have not been activated. According to a patient's clinical history, it might be possible to classify a patient using objective clinical criteria that is easy to register and that has predictive value.

CASE PRESENTATIONS

Patient 1

Patient 1 was a 35-year-old woman with no personal or family history of clinical interest, except primary infertility. Follitropin beta 50 UI was prescribed for the treatment of infertility. On the second day of treatment, the patient started to feel acute pain in her forearms and stiffness in both hands that prevented her from performing simple daily activities and tasks, such as holding cutlery. The patient's symptoms progressively worsened, and over the course of 9 months, other symptoms developed, such as cervical pain, orthostatic intolerance, digestive discomfort, livedo reticularis, leg pain, difficulty walking and climbing stairs, mental "fog," and exercise intolerance.

The patient was referred to a department of internal medicine, where pathologic findings were reported on capillaroscopy. Based on that study and her symptoms, the first diagnostic suspicion was polyarteritis nodosa. To confirm the diagnosis, several additional tests were performed, briefly: analytics with autoimmunity markers, electromyography, nuclear magnetic resonance, esophageal manometry, mesenteric arteriography, and muscle biopsy. All test findings were normal; therefore, the diagnostic suspicion was not confirmed, and other autoimmune diseases were also ruled out.

Over the next 2 years, the patient was evaluated by several specialists: a neurologist, orthopedic surgeon, rheumatologist, pain specialist, and psychiatrist. She was diagnosed with fibromyalgia and neuronally mediated hypotension. Eventually she visited a rheumatologist with knowledge on ME/CFS, who diagnosed this pathology by applying the international consensus criteria (2011).[12] There was a 3-year delay before diagnosis, during which the patient had several "crash effects" that kept her bedridden for months and in need of a wheelchair. After diagnosis, pain treatment was duloxetine 60 mg once daily and gabapentin 300 mg q8h, in addition to the following nutritional supplements (in alternating periods every 3–4 months): coenzyme Q, NADPH, ribose, L-acetyl carnitine, vitamin D, and vitamin B_{12} IM. There was a slight improvement; currently (5 years from the onset of the disease) her situation is stable. The patient can leave home,

although a wheelchair is necessary for walking more than 5–10 min. Her degree of current disability, according to the Bell scale, is 4 (moderate symptoms at rest, moderate to severe symptoms with exercise or activity, and overall activity level reduced to 50%–70% of expected, able to go out once or twice per week, unable to perform strenuous duties, and able to work at home, while seated, for 3–4 h/d, but with required rest periods).

Patient 2

Patient 2 was a 34-year-old woman with no personal history of clinical interest. She had a family history: Her mother had ataxia and physical limitation, diarrhea, and asthenia without diagnosis when Patient 2 presented to the clinic. Subsequently, the mother was diagnosed with ME/CFS.

The patient began to visit health care professionals after her first child's birth, due to a significant weight loss over a period of 12 months (about 10 kg of her usual weight before pregnancy). Later she began to experience pain and functional impotence in her right leg. Over a period of 12 months, further symptoms appeared: upper limb pain, migraines, syncope, tachycardia, orthostatic intolerance, visual disturbances, mental "fog," and exercise intolerance.

The initial clinical suspicion was mitochondrial disease versus metabolopathy. To confirm the pathology, a muscle biopsy was performed; the test indicated normal parameters. Then, a complete study of metabolopathies was done. All test findings were normal; thus no diagnosis was provided.

After 4 years of symptomatology and numerous visits to health care providers (a neurologist, ophthalmologist, internist, and digestive health specialist), many diseases of genetic basis were ruled out. During this period, the patient was diagnosed with fibromyalgia and irritable bowel syndrome. She eventually received a correct diagnosis from a neurologist who specialized in neuromuscular disease and with knowledge of ME/CFS, who applied the international consensus criteria and diagnosed ME/CFS.[12] The prescribed treatments were duloxetine, pregabalin, methylphenidate, and gabapentin. However, all treatments were suspended due to intolerance. Therefore, there was no prescribed long-term treatment with the exception of those required for migraine and pain: diazepam, dexketoprofen, and eletriptan. The patient's condition has progressed, with the patient able to walk only a few steps and requiring an electric wheelchair. Her degree of current disability, according to the Bell scale, is 2 (moderate to severe symptoms at rest, unable to perform strenuous activity, overall activity 30%–50% of expected, unable to leave home except rarely, confined to bed most of the day, and unable to concentrate for >1 h/d).

Patient 3

Patient 3 was a 38-year-old woman with a personal history of obesity and no family history of clinical interest.

After several consecutive respiratory infections, this patient experienced a severe one that was diagnosed as infectious mononucleosis (immunoglobulin M positive), the patient did not recover from this infection, which presented from the beginning with intense asthenia and polymyalgia. Over the subsequent months, other symptoms developed, such as orthostatic intolerance, mental "fog," exercise intolerance, and a total weight loss of 34 kg.

The initial clinical suspicions were obesity, anemia, hypothyroidism, and infectious disease. A complete analytical study was done. The patient was evaluated by an internist, neurologist, rheumatologist, and endocrinologists. All test findings were normal. The patient was also diagnosed with fibromyalgia. After 2 years of progression, and after infectious and metabolic diseases were ruled out, the patient was evaluated by a primary care physician with knowledge of ME/CFS, who, applying the international consensus criteria, diagnosed ME/CFS.[12] The indicated treatments were duloxetine and pregabalin for pain and occasionally supplementation with vitamin D and vitamin B_{12} IM. The patient's condition has progressed. She requires an electric wheelchair. Her degree of disability according to the Bell scale is 3 (moderate to severe symptoms at rest, severe symptoms with any exercise, overall activity level reduced to 50% of expected, usually confined to the home, unable to perform any strenuous tasks, and able to perform desk work for 2–3 h/d, but with required rest periods).

DISCUSSION

The lack of skills required to identify ME/CFS and the nonspecific features of this condition make it difficult

to suspect this pathology. It can take years to obtain a ME/CFS diagnosis, which can be painful for patients and at the same time prevents health care professionals from providing adequate treatment. The fact that this disease has symptoms that overlap with those of other conditions makes it necessary to rule them out before reaching a diagnosis. In the cases reported here, it took from 2 to 4 years to receive the right diagnosis. Thus, it is important that health care providers develop adequate skills to facilitate the diagnosis and management of the disease.

The initial clinical suspicion in the cases reported here, was done based on the symptoms at the onset of the disease, and mainly taking into account a) the trigger: drug administration (Patient 1), the postpartum (Patient 2) or an infection (Patient 3); b) either localized (Patient 1 and 2) or generalized (Patient 3) affectation, c) having a family background (Patient 2 only). The variability in the symptoms from patient to patient led to 3 different initial clinical suspicions, namely, immunologic/autoimmune disease (Patient 1), inherited/mitochondrial disease (Patient 2), and metabolic/infectious disease (Patient 3). Therefore, patients were referred to different specialist physicians. Over a 1- to 2-year period, new symptoms developed, and the 3 patients started to share some of them. At this point, and after other pathologies were ruled out and the patients had visited health care professionals with knowledge on ME/CFS, the diagnosis in the 3 cases was ME/CFS.

A retrospective analysis of these 3 clinical cases shows that, although after years of progression these patients had similar manifestations and shared symptoms, the onsets were rather different. Interestingly, the 3 initial clinical suspicions correlated with 3 mechanisms that have been studied in ME/CFS. Moreover, they have been considered as possible indicatives of different subgroups of ME/CFS. Thus, it might be important to consider the information we have at the onset of the disease, as it might be of interest, as an aid in the clustering of patients.

In clinical practice, the clinical records of patients with ME/CFS are not typically thoroughly explored as a source of information and, as indicated earlier, might be an important point to take into consideration. If we analyze the 3 clinical cases presented here, currently the degree of disease severity is different in each patient, and each also presented with different comorbidities (fibromyalgia [all 3 cases], neuronally mediated hypotension [Patient 1], and irritable bowel syndrome [Patient 2]). Interestingly, it has been pointed out that patients with ME/CFS and irritable bowel syndrome might be considered a ME/CFS subgroup.[13]

In the past decade, different groups and researches have pointed out the presence of factors that might be of importance in classifying patients with ME/CFS. Clustering those patients who share the same conditions will aid in the interpretation of research data and in the provision of effective treatment. Clinicians could contribute to the classification of patients with many years of progression through clinical histories. It would be of interest to establish a standardized clinical record and to register relevant parameters, including: (1) the trigger mechanism; (2) onset, and whether there was a localized or generalized affectation; (3) existence of family history; (4) degree of disability, both subjective measures obtained through typified questionnaires, Bell scale, or similar, as well as other, more objective parameters, such as hours of sleep, hours of rest, and number of daily steps, in order to achieve greater reproducibility; and (5) comorbidities, such as fibromyalgia, irritable bowel syndrome,[13] symptoms of possible mast cell activation,[14,15] neuronally mediated hypotension, and orthostatic postural tachycardia.

To decrease the time to diagnosis, which would also facilitate data collection, physicians must be trained in the pathology of ME/CFS. It would be necessary to create centers for referral, where patients would receive a proper diagnosis and follow-up. These centers should also be involved in research. In addition, reference centers should network with the clinicians who care for the patient in their place of residence, which would reduce visits to reference centers, and at the same time ensure that all patients receive the most appropriate care, as their physicians would have the required information. A network among reference centers will also contribute to the advancement in the knowledge of the pathology of ME/CFS.

CONCLUSIONS

The 3 cases reported here highlight the need for clinician training to obtain early diagnosis and better management of ME/CFS. This will also provide samples in the early stages of pathology. The three cases reported highlight the need of a better medical training to get early diagnosis and a better management of the disease, and in this way it will be also possible to get samples in the early stages of the pathology. Interestingly, in these clinical cases, the onset correlate with several of the different approaches researches followed: immune, inflammatory, genetic or metabolic disease. Therefore, clinicians can contribute to the generation of subgroups of ME/SCF patients based on clinical presentation and the occurrence of comorbidities. To this aim, a complete clinical history should be obtained and a minimum of variables should be registered: triggers, onset, localized or generalized affectation, existence of family history, degree of disability, and comorbidities.

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E. Martín-Martínez conceived of this case report, revised it critically for intellectual content, conducted the literature review, drafted the manuscript, and gave final approval of the version to be published. M. Martín-Martínez contributed to manuscript writing and preparation.

CONFLICTS OF INTEREST

The authors have indicated that they have no conflicts of interest with regard to the content of this article.

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Address correspondence to: Dr. Eva Martín-Martínez, Manises Hospital, National Health Service, Cierva 3, Valencia 28006, Spain. E-mail: evamariamartinmartinez@gmail.com