The Diagnosis and Management of Chronic Inflammatory Demyelinating Polyneuropathy (CIDP) when it is Comorbid in Patients with the Fibromyalgia Syndrome (FMS): A Focused Review

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Abstract

The central neurologic soft tissue pain condition, called fibromyalgia syndrome (FMS), and the autoimmune peripheral nerve injury condition, called chronic inflammatory demyelinating polyneuropathy (CIDP), are both potentially disabling. Either condition can accompany an arthritis condition. The general population prevalence of FMS is about two percent, while CIDP is less common, at less than one percent. On this basis, overlap (being comorbid) of FMS and CIDP by chance would be expected in about two per ten thousand of the general population or in about one percent of persons with FMS. By contrast, these conditions are reported to be comorbid (i.e., FMS/CIDP overlap) in thirty percent of FMS. This high level of association between FMS and CIDP has not yet been adequately explained. Fortunately, validated diagnostic criteria are available for both conditions so they can be distinguished from each other on the bases of established clinical criteria. A self-report questionnaire, based on the 2010 American College of Rheumatology Fibromyalgia Diagnostic Criteria can be used as support for the clinician's diagnosis of FMS (sensitivity ninety six percent). CIDP can be diagnosed using the electrophysiology-based European Federation of Neurological Societies/Peripheral Nerve Society criteria (sensitivity ninety six percent). Neurologic consultation is key to the diagnosis of CIDP. Lower extremity weakness and/or hyporeflexia in a patient with FMS should prompt consideration of FMS/CIDP. Many or all of the chronic manifestations of FMS/CIDP can improve with a course of intravenous immunoglobulin. There are potential risks associated with intravenous immunoglobulin therapy, but clinicians and patients will often conclude that the severity of the impairment associated with FMS/CIDP justifies some therapeutic risk. The threshold for treatment of FMS/CIDP should be low because the potential for benefit is high.

Keywords: Fibromyalgia syndrome; Chronic inflammatory demyelinating polyneuropathy; Intravenous immunoglobulin therapy

Abbreviations:

FMS: Fibromyalgia Syndrome; CIDP: Chronic Inflammatory Demyelinating Polyneuropathy; IVIG: Intravenous Immunoglobulin Therapy

Introduction

The fibromyalgia syndrome (FMS) is believed to be a central neuropathic condition with peripheral manifestations (symptoms), while chronic inflammatory demyelinating polyneuropathy (CIDP) is considered to be mainly a peripheral neuropathic condition. Both of these conditions have the potential to physically impair affected individuals and even lead to disability. The natural history of both conditions is to persist if untreated. It should not come as a surprise that these two relatively common disorders can occasionally coexist (be comorbid) in the same patient. It has become a common practice to identify FMS as either 'primary FMS' or 'secondary FMS'. Primary FMS is viewed as having presented in a clinically isolated form, while secondary FMS presents in the setting of another readily-definable condition, particularly an inflammatory disorder, whether or not there is any evidence that the associated disorder has, in any way, contributed in the development or pathogenesis of the FMS.

In a study reported by Caro et al. [1], CIDP was observed to occur in about one third of adult FMS patients. When these conditions do coexist, they can be viewed as being comorbid with each other and the combined pattern of symptoms would be expected to result in even greater impairment potential for the affected patient than would typically be evident with either condition separately. As with the emergence of overlapping drug side effects, when two drugs are given to a single individual, some of the unique manifestations of each disorder (FMS, CIDP) would be expected to emerge when both conditions are comorbid in a single individual (eg, FMS/CIDP).

The driving force behind seeking the comorbid diagnosis of CIDP in patients with FMS is also embodied in the findings of Caro et al. [1]. They observed that in patients who had both conditions, many of the chronic manifestations associated with both conditions improved, or were eliminated, by the administration of a course of intravenous immunoglobulin (IVIG). Adverse events that have been associated with IVIG therapy have included systemic reactions such as fever, nausea, vomiting, tachycardia, dyspnea, changes of blood pressure, hypersensitivity, even anaphylactic reactions in persons with IgA deficiency [2-11]. Other potential risks can include haemolytic anaemia, thrombosis leading to embolization, headache, relapsing aseptic meningitis syndrome, and osmotic nephrosis [2-11]. Asymptomatic laboratory changes and transmission of the hepatitis C virus may be possible, the more serious complications have been relatively rare, and their relationships to IVIG administration are still

controversial. Some authors have advocated patient pretreatment before infusion to help avoid minor systemic reactions [7]. While there are potential risks associated with IVIG therapy, its use in the treatment of patients with CIDP is considered to be relatively safe [12,13]. Most clinicians and patients will conclude that the severity of the impairment associated with FMS/CIDP justifies the acceptance of at least some potential therapeutic risk. In a recent study of CIDP therapy, it was documented that pharmacy charges represented the highest portion (57%) of the overall therapeutic costs of CIDP treatment and IVIG accounted for 90% of those pharmacy-related costs [14].

When the clinician is considering an association of CIDP with FMS, it is important that the clinician use the CIDP diagnostic criteria which are known to have the greatest probability (highest sensitivity) of identifying CIDP. Given two relevant scenarios (seeking CIDP cases among a population of FMS patients or seeking evidence for comorbid CIDP in the care of an individual FMS patient), the sensitivity of the diagnostic criteria used to identify the comorbid CIDP should be viewed as being more critical than would be the specificity of those criteria. Stated otherwise, if a relatively safe treatment is available for a clinically devastating condition such as comorbid FMS/CIDP, it is important to identify as many cases with that condition as possible, so a higher proportion of affected individuals can benefit from relatively safe therapy. To date, there is no evidence that primary FMS will benefit from a course of IVIG. Despite that, it may be better to administer IVIG to an occasional patient with a variant form of primary FMS than to miss the opportunity to treat a patient who actually has FMS/CIDP. Of course, accuracy of the CIDP diagnostic approach increases the likelihood of a beneficial therapeutic response.

Case Report

A 69 year old divorced female, retired accountant presented with a 40+ year history of fairly mild fibromyalgia syndrome (FMS). Her initial symptoms had begun at about age 24 with neck pain, shoulder pain, and intermittent fatigue, and then persisted for many years. The diagnosis of FMS was made when she was 32 years of age, shortly after she was forced to admit that she was failing financially in her attempt to operate a restaurant. Even though her FMS symptoms had already been present for eight years, her FMS was attributed to the acute stress. Therapeutic interventions at the time were not helpful in relieving any of her symptoms. At about age 46, she was treated for hypertension and became aware that she was sleeping poorly. Polysomnography demonstrated over 50 apneic or hypopneic episodes per hour during which oxygen saturation fell to less than 80%. A new diagnosis of obstructive sleep apnea (ASO) was made. Recall the known association of systemic hypertension with ASO [15]. Continuous positive airway pressure (CPAP) therapy was prescribed for her, but she did not tolerate any of the face masks made available to her and unwisely gave-up on the CPAP intervention. At about age 62, she developed what she described as a "widespread neurosensitivity episode". Her perception was that her nerves extended well beyond the confines of her skin and caused a sensation that felt as if her skin was on fire. She became unsteady on her feet. Her neurologist conducted extensive electrophysiology testing and found evidence for a large fiber peripheral neuropathy but he was uncertain regarding which of her symptoms could properly be attributed to her previously diagnosed FMS. She tried several treatments but "nothing cooled the burning pain". She took a non-steroidal anti-inflammatory drug for several

months but it was eventually discontinued because she developed an analgesic nephropathy.

On examination, she was slender but appeared to be well nourished (BMI=23.5). Her vital signs were normal. She was not aware of having become weak, but she could not rise from a chair without assistance from the examiner. There was some discomfort in the lower part of her body but she did not believe that the discomfort impacted her ability to stand. Her lower extremity muscles were diffusely weak but her upper extremity strength was nearly normal. Her abdomen was protuberant when standing but scaphoid when she was recumbent. In the recumbent position, the abdominal musculature was nearly flaccid, even when she attempted to lift her head. The thickness of her abdominal wall was only about 1.5 inches (3.8 cm), so the flaccidity was not due to abundant adipose. Although she complained of dysesthesia, her sensory examination to light touch was normal. Her Romberg test was normal but she walked with wider-based gait than normal. Her gait was too unsteady to attempt a tandem gait test.

Deep tendon reflexes were diffusely hypoactive. Babinski testing was negative for toe flair bilaterally, but on stimulation of the right sole, she involuntarily withdrew the left leg because of pain referred to the left groin associated with the plantar stimulus.

One persistently-actionable problem for her was the failed OSA therapy, so she was referred for repeat polysomnography in the hope that newly-available devices might improve her compliance with CPAP for the OSA. In addition, she was given presumptive diagnoses of overlap FMS/CIDP. She was referred back to her neurologist to determine whether he could now confidently attribute her large fiber peripheral neuropathic findings to CIDP. If the neurologist agrees, the plan in this patient would be to try a course of IVIG therapy for comorbid FMS/CIDP.

Discussion

In the above case, the physician's attribution of the patient's FMS symptoms to stress represented an inadequately-informed causal integration. Stresses in the lives of FMS patients are no more numerous, nor more severe, than in healthy normal people without FMS The stress-related physiological defect which actually pertains to FMS is a hypothalamic-pituitary-adrenal (HPA) dysfunction which can be caused by the abnormally elevated substance P levels in FMS [16]. Substance P is believed to inhibit the function of the HPA-glucorticoid stress-response axis [17,18].

Recognizing the potential variability of the presentation of each of the conditions (FMS, CIDP) relevant to this discussion, it would be expected that the presentation of FMS/CIDP would be variable from one to another affected patient. The key to considering CIDP overlap with FMS in this case was the observation that the patient exhibited profound weakness of her lower extremity and abdominal muscles. As expected in CIDP, this patient's weakness was substantially more severe than was her sensory dysfunction. Patients with primary FMS may have some difficulty with rising from a sitting position, but the cause is usually a combination of pain and generalized deconditioning. In this case the patient did not attribute her difficulty in standing from the seated position to lower extremity pain and her upper extremity strength was very adequate for age. The neurologist's electro diagnostic finding of a large fiber neuropathy supports the presumptive diagnosis of CIDP in overlap with the patient's long-term FMS. The rheumatologist's view was that she may have an overlap FMS/CIDP

syndrome [1]. It is not yet certain that the neurologist will agree with the rheumatologist's view, but it is likely that he will do so.

It is reasonable to ask whether misdiagnosis can be an issue in patients with FMS and/or CIDP. It would be naive to doubt that misdiagnosis in all three directions (CIDP as FMS, FMS as CIDP, FMS/CIDP as FMS or CIDP alone) could occur. Patients with FMS can become weak because they have pain and are inclined not to participate in regular exercise. Some patients with CIDP can experience widespread somatic pain, which does not necessarily represent an overlap with FMS but could represent autoimmune injury to sensory as well as motor fibers? Patients with FMS tend to be hyperreflexic or even to exhibit cocontraction [19,20]. The potential overlap between these two conditions is sufficiently high that FMS patients with weakness and/or hyporeflexia should be tested for CIDP and patients with CIDP having somatic pain should be interrogated for evidence to document FMS diagnostic criteria. Only about 50% of FMS patients meet efficacy response criteria when treated with a single medication from among the medications approved by the United States Food and Drug Administration (FDA) for this indication [21,22]. Could the underlying reason for that discrepancy be a common misdiagnosis of variant CIDP as FMS? The answer to that question is not likely to come by accident. Since treatment modalities that are successful for CIDP are different than those already approved for patients with FMS, patients with overlap FMS/CIDP will be best served by thoughtful consideration of all three potential diagnoses.

Obstructive sleep apnea (OSA) is not the characteristic sleep dysfunction exhibited by patients with primary FMS [23-25], but OSA has been fairly commonly found in overlap with FMS (45% in one study, among FMS and non-FMS patients referred for polysomnography. On the other hand, there was no difference in prevalence of OSA by diagnosis group) [26].

The following paragraphs offer clinical descriptions and characterizations of FMS, CIDP and FMS/CIDP.

Fibromyalgia syndrome (FMS)

FMS clinical manifestations

Fibromyalgia syndrome (FMS) is a chronic illness characterized by chronic widespread pain, areas of somatic tenderness called tender points, and sleep dysfunction, but it can also exhibit fatigue, cognitive dysfunction, depression, anxiety, and upper extremity dysesthesia which resembles carpal tunnel syndrome. The widespread pain and low pain threshold (allodynia) will be variably present in some but not all FMS patients. For example, sleep dysfunction is present in 70-95% of FMS patients but depression is found in only one third [27]. There is some selection bias for specific comorbidities to be represented depending on the specialty or focus of the clinicians studying the recruited population. For example, a sub-population of FMS patients being evaluated in a psychiatric clinic will likely exhibit a higher prevalence of depression and other psychiatric comorbidities than would that being diagnosed in a general internal medicine clinic or rheumatology practice. Similarly, upper extremity dysesthesia may be particularly common among FMS patients presenting to an orthopedic hand clinic because primary care physicians tend to refer their patients with a presumptive diagnosis of carpal tunnel syndrome to orthopedists.

FMS diagnosis

For many years, the diagnosis of FMS was based on the 1990 American College of Rheumatology Research Classification Criteria (1990 ACR RCC) which relies entirely on the characteristic widespread pain and tenderness aspects of FMS [28]. These criteria were originally designed for diagnosis of patients to be enrolled in clinical research studies, but they were never validated for use in clinical care settings. Despite that, many clinicians used these criteria in the clinical care setting as well. Unfortunately, some clinicians did not apply the required methodology in a systematic manner. Concern was raised because differences in diagnostic criteria resulted in different subpopulations of patients receiving the diagnosis of FMS [29]. For these and other reasons, the 1990 ACR RCC was perhaps unjustly censored by many authors. Alternative criteria (2010 ACR Fibromyalgia Diagnostic Criteria, 2010 ACR FDC) were developed and validated for use in the clinical setting [30]. The new 2010 ACR FDC required a systematic interview of the patient with the health care professional, so it was still time-consuming. However, it offered the advantage of assessing information about several of the non-pain-related comorbid manifestations of FMS. These criteria utilized two composite scores called the Widespread Pain Index (WPI) and the Severity of Symptoms Scale (SSS) score. Since the 2010 ACR FDC are easier to use than were the 1990 ACR RCC, it was anticipated that these new criteria will be applied more accurately than the 1990 ACR RCC and would prove to be more reliable in clinical practice. Using these newer criteria, the diagnosis of FMS is facilitated with a range of outcome values from a WPI of ≥ 7 and an SSS of ≥ 5 to a WPI 3-6 and an SSS of ≥ 9. For a diagnosis of FMS, the symptoms must have been present for at least 3 months and there must not have been a recognized co-morbid condition which could account for all of the symptoms. In a subsequent study, many of the same authors reported an even more simplified approach in which the critical data for a diagnosis of FMS could be obtained using a one-page self-report questionnaire (Table 1). In the questionnaire format, the physician could make the diagnosis of FMS if the composite score for a given person and time was (WPI plus SSS ≥ 13) [31].

Jaw, Rt.	Upper Arm, Rt.	Upper Back	Upper Leg, Rt.
Jaw, Lt.	Upper Arm, Lt.	Lower Back	Upper Leg, Lt.
Neck	Lower Arm, Rt.	Hip [buttock, trochanter], Rt.	Lower Leg, Rt.
Shoulder girdle, Rt.	Lower Arm, Lt.	Hip [buttock, trochanter], Lt.	Lower Leg, Lt.
Shoulder girdle, Lt.	Chest	Abdomen	N/A

Table 1A: 2010 American College of Rheumatology Fibromyalgia Diagnostic Criteria Self-Report Questionnaire. Widespread Pain Index [WPI, Score 0-19]

Time period of Focus: During the past two weeks. Instructions: Check each body site that has been painful during the past two weeks

Tiredness in the morning	[0-3 severity, 0=None, 1=Slight/mild, 2=Moderate, 3=Severe]
Fatigue through the day	[0-3 severity, 0=None, 1=Slight/mild, 2=Moderate, 3=Severe]
Dyscognition	[0-3 severity, 0=None, 1=Slight/mild, 2=Moderate, 3=Severe]
Somatic symptoms	[0-3 scale, # of other symptoms: 0=None [0], 1=few [1-9], 2=mod [10-29], 3=many [30+]

Table 1B: Symptoms Severity Score [SSS, range 0-12]

Instructions: For each of the next three items, circle the symptom severity that applies. Circle each item that has been symptomatic in the past two weeks.

Muscle Pain, Irritable bowel syndrome, Fatigue/Tiredness, Thinking or remembering problem, Muscle Weakness, Headache, Pain/cramps in abdomen, Numbness/Tingling, Dizziness, Insomnia, Depression, Constipation, Pain in upper abdomen, Nausea, Nervousness, Chest Pain, Blurred vision, Fever, Diarrhea, Dry Mouth, Itching, Wheezing, Raynaud's, Hives/Welts, Ringing in ears, Vomiting, Heartburn, Oral ulcers, Loss/Change in taste, Seizures, Dry eyes, Shortness of breath, Loss of appetite, Rash, Sun sensitivity, Hearing difficulties, Easy bruising, Hair Loss, Frequent urination, Painful urination, and Bladder spasms [30,31].

As discussed in the Introduction, the concept of primary and secondary FMS must be understood. It was indicated that primary FMS can be viewed as having presented in a clinically isolated form with the only comorbidities being those typically associated with FMS. By contrast, secondary FMS presents in the setting of another readily-definable clinical condition [often an inflammatory or autoimmune disorder] whether or not there is any evidence that the associated disorder has, in any way, contributed to the development or pathogenesis of the FMS. Other medical conditions known to overlap with FMS include rheumatoid arthritis (about 20% of RA), systemic lupus erythematosus (FMS up to 40% of SLE; a Mexico City study reported 9.5%) [32], Sjögren's syndrome (FMS in about 20-50% of SjS) and CIDP (CIDP in about 30% of FMS).

The research study which established the 1990 ACR RCC included some patients with secondary FMS. It was noted in that report that there were no important clinical differences in the FMS manifestations of primary and secondary FMS, so it was recommended that the designations "primary FMS and secondary FMS" be abandoned [28]. It turned out that they were not generally abandoned for at least four reasons, 1. Because they provided a useful categorization that has been heavily relied upon in the recruitment of FMS patients for pharmacologic clinical trials (to date, clinical trials have endeavored to recruit only primary FMS), 2. Because the signs and symptoms experienced by patients with secondary FMS are likely to be influenced by the comorbid disorder, 3. Because the reported manifestations of secondary FMS will be influenced by the focus of the physician specialty providing care for- or studying that comorbid disorder, and 4. Because primary and secondary FMS are indeed biologically different conditions with different biochemical pathogenesis [33], with regard to item #3 above. The comorbid disorder of note for the current treatise is CIDP and the physician specialty of note would be neurology.

FMS epidemiology

The signs and symptoms of FMS can present at any age but they are found more typically in adult women (F) than in adult men (M, ratio F9:M1) with an average age ranging between 40 and 50 years at diagnosis [34]. It is estimated that in the United States the prevalence of adult FMS is about 2% of the general population but that number increases by decade until nearly 10% of adult women in their 6th decade of life have FMS [34,35]. Based on this prevalence number and the United States population at the time, Lawrence et al. estimated that there were about 5 million adults with FMS in the United States [36]. Fibromyalgia can also affect children and adolescents. A study in Mexico City identified juvenile FMS in children ages 9-15 years and estimated the prevalence of juvenile FMS to be 1.2% [37].

FMS management

In 2007, Chakrabarty summarized a contemporary view of treatment options for FMS to include pain management, anti-depressive medication, and cognitive behavioral therapy and exercise [38]. More recently, secondary research, including meta-analyses and reviews, have led to guidelines for use by patients and physicians to plan the management of FMS. For example, the American Pain Society recommendations included cognitive-behavioral therapy, aerobic exercise, amitriptyline, and multi-component therapy [39]. The European League against Rheumatism offered a recommendation based only on pharmacologic treatment (amitriptyline, tramadol, fluoxetine, duloxetine, milnacipran, moclobemide, pirlindole, Tropisetron, Pramipexole, or pregabalin) for FMS [40].

A recently reported metaanalysis [41] characterized the efficacy profiles of pharmacologic and non-pharmacologic interventions with a clear focus on the six core FMS clinical domains, as defined by OMERACT (pain, sleep dysfunction, fatigue, depression, physical dysfunction, cognitive dysfunction) [42,43]. In addition, that metaanalysis report identified potential combinations of pharmacologic and non-pharmacologic interventions, in hopes that future study may prove them to be complementary in treating patients with multi-symptomatic FMS.

In order to achieve FDA approval for the FMS indication, a medication must have been found to be relatively safe in primary FMS patients and to exhibit significantly more benefit than was provided by placebo. Unfortunately, none of the three drugs which have met those criteria to date have, in monotherapy, provided what is defined as clinically relevant improvement for more than about 50% of patients [21,22]. That observation must raise some doubt that the FMS population is really as homogeneous as it once appeared to be. Indeed, it is exactly what would be expected if a substantial proportion of the studied FMS patients were misdiagnosed or had unrecognized secondary FMS with a comorbid condition, such as CIDP, that is unresponsive to those medications.

Chronic Inflammatory Demyelinating Polyneuropathy (CIDP)

CIDP clinical manifestations

Some clinicians consider CIDP to be the chronic form of the acute idiopathic polyneuropathy known as Guillian-Barré syndrome (GBS) [44-48]. Both conditions are thought to be acquired autoimmune disorders. Features of CIDP include "progressive, symmetric, proximal and distal muscle weakness, variously accompanied by paresthesia, sensory dysfunction, and impaired balance. The symptoms tend to evolve slowly over two months or more [49]. The common CIDP variants include unifocal, multifocal, pure motor, pure sensory, sensory ataxic and pure distal forms [50]. With the potential for such a variable clinical presentation, it is not surprising that diagnosis based solely on clinical signs and symptoms is difficult. The characteristic large fiber sensory loss and areflexia can suggest multifocal disease. CIDP may or may not have an associated pain component [51]. A 2009 study demonstrated that the majority of CIDP patients exhibited a decrease in functional status, fatigue, and impairment as represented by lower scores on the SF-36 [52]. The duration of CIDP-related symptoms prior to diagnosis can range from 1.4-11.5 years [12]. This prolonged incubation time may negatively impact the ultimate clinical course for the patient resulting in substantial physical dysfunction and a poor quality of life [12,53-55].

CIDP Diagnosis

As mentioned above, the diagnosis of CIDP can be challenging because its onset is typically insidious and its manifestations can mimic many other medical/neurological disorders [56-65].

In 1975, Dyke et al., were among the first to describe criteria for the diagnosis of CIDP, which included aspects of the clinical course (≥ 8 weeks of progressive weakness and other symptoms); the type of nerve fiber class affected (large nerve fibers) and the symmetry of distribution [64]. Several more recent criteria have been developed for the diagnosis of CIDP, to include data from clinical manifestations, electrodiagnostic studies, imaging, cerebral spinal fluid analysis, and/or pathology from nerve biopsy [49,56,57,66]. These studies were variously conducted and/or espoused by the American Association of Neurology (AAN), the European Federation of Neurological Societies (EFNS), the Inflammatory Neuropathy Cause and Treatment (INCAT) study group, and the IGIV-C CIDP Efficacy (ICE) study group.

A relatively unusual approach used by one diagnostic criteria study was to seek a consensus of experts in the form of a Delphi exercise and then to define that consensus as the gold standard [67]. They justified their approach as follows: "Although this gold standard is fallible and vulnerable to criticism, in the absence of a reliable biological marker, this is currently the best surrogate of CIDP status" [67]. Subsequently, most authors have emphasized the value of objective electrodiagnostic and pathological findings in the diagnosis of CIDP [58,67-69].

A European multicenter comparison study utilized 151 CIDP patients and 162 controls to judge the effectiveness of the available criteria for making the diagnosis of CIDP [69]. The authors found the European Federation of Neurological Societies/Peripheral Nerve Society (EFNS/PNS) criteria to offer a high sensitivity (96%) and a reasonable specificity (79.3%). It is important to point out that the EFNS/PNS criteria for diagnosis of CIDP (Table 2) are based almost exclusively upon the relatively non-invasive electrodiagnosis of candidate patients and do not require histology [70].

"Definite CIDP": at least one of the following	"Probable CIDP"	"Possible CIDP"
A. At least 50% prolongation of the motor distal latency above the upper limit of normal values in two nerves, or	At least 30% amplitude reduction in the proximal negative peak CMAP relative to distal, excluding the posterior tibial nerve, if distal negative peak CMAP at least 20% of lower limit of normal values in two nerves, or in one nerve + at least one other demyelinating parameter in at least one other nerve	As in "I" but in only one nerve
A. At least 30% reduction in motor conduction velocity below the lower limit of normal values in two nerves, or		
C. At least 20% prolongation of F-wave latency above the upper limit of normal values in two nerves [.50% if amplitude of negative peak compound muscle action potential [CMAP] ,80% of lower limit of normal values], or		
D. Absence of F waves in two nerves if these nerves have amplitudes of distal negative peak at least 20% of lower limit of normal values + at least one other demyelinating parameter in at least one other nerve, or		
E. Partial motor conduction block: at least 50% amplitude reduction in the proximal negative peak CMAP relative to distal, if distal negative peak CMAP at least 20% of lower limit of normal values, in two nerves, or in one nerve + at least one other demyelinating parameter in at least one other nerve, or		
F. Abnormal temporal dispersion [30% duration increase between proximal and distal negative peak CMAP] in at least two nerves, or		
G. Distal CMAP duration [interval between onset of the first negative peak and return to baseline of last negative peak] of at least 9 ms in at		

least one nerve + at least one other demyelinating parameter in at least one other nerve		

Table 2: EFNS/PNS electrodiagnostic criteria for chronic inflammatory demyelinating polyneuropathy (CIDP) [71].

Abbreviations used above:

(EFNS/PNS) represents European Federation of Neurological Societies/Peripheral Nerve Society

(CIDP) represents Chronic Inflammatory Demyelinating Polyneuropathy

(CMAP) represents Compound Muscle Action Potential

In a British study [71], the authors compared the AAN Criteria with the EFS/PNS Criteria. The prevalence of CIDP fulfilling the 2006 clinical and electrophysiologic EFNS/PNS criteria was 4.77 per 100,000 (95% confidence interval = 3.49-6.37). Using the 1991 American Academy of Neurology (AAN) criteria on the same population of patients, the prevalence was 1.97 per 100,000 (95% CI = 1.19-3.08). Lewis-Sumner variant syndrome was diagnosed in 15.2% of patients and 23.9% of those had a pure sensory onset. Over 40% of CIDP patients required no immunotherapy, and 84.6% of those treated achieved clinical response. The mean annual incidence rate over a 3-year period was 0.70 per 100,000/year using EFNS/PNS criteria (95% CI 0.43-1.08), and 0.35 per 100,000/year using AAN criteria (95% CI 0.17-0.64). They concluded that the AAN criteria substantially underestimated the prevalence and incidence of CIDP. The EFNS/PNS criteria provided higher diagnostic sensitivity than did the AAN criteria. Furthermore, the EFNS/PNS criteria were judged to be of greater clinical relevance, in-part, because they offered a useful breakdown of the epidemiologic data for CIDP subtypes [71].

The criteria used by Caro et al. in their search for a CIDP-like illness in people with FMS included lower extremity stocking hypaesthesia (hypoesthesia), proximal muscle weakness in at least two extremities, and electrodiagnostic evidence of a demyelinating polyneuropathy [1]. They indicated that their criteria closely resembled the INCAT criteria [58].

CIDP epidemiology

The CIDP syndrome is a chronic illness with a prevalence in the general population of up to 8.7/100,000 persons according to Hughes [12]. Men [M], between the ages of 30-60, are more likely than are women (F, ratio, M1.3:F1) to be diagnosed with CIDP [72] but that difference in prevalence by gender is rather trivial when considering this diagnosis of CIDP in clinical practice. Most of what is known about the prevalence, incidence, and natural history of CIDP comes from two studies, one conducted in Italy [72] and the other in the United Kingdom [71]. In the Italian study [72], the authors used the research criteria of the American Academy of Neurology, which a later study found to have poor sensitivity (45.7%) despite its high specificity (100%) [69]. Of the 294 patient studied, 165 met the AAN research diagnostic criteria. The crude prevalence rate was 3.58/100,000 population (95% CI 3.02 to 4.20). At the time of diagnosis, 76 (49.0% of all cases) had definite and 67 (43.2% of all cases) had probable CIDP. Disability was severe in 18 (11.6%), moderate in 32 (20.6%), but the majority 105 (67.7%) had only mild limitation. The course was chronic-progressive in 96 (61.9%), remitting-relapsing in 40 cases (25.8%), and monophasic in 19 (12.3%). The mean annual crude

incidence rate was 0.36/100,000 population (5% CI 0.29 to 0.44), with a male to female ratio of 2.3:1. Only 14 cases (8.5%) had diabetes mellitus. In multivariate analysis, factors related to severe disability were: age >60 years, failure of immunomodulation therapies at the time of diagnosis, worse impairment, and a chronic course.

CIDP management

In the past 30 years, there has been a progressive shift in the contemporary understanding of the pathogenesis and management of CIDP [49,73,74]. Since the contemporary approach to the most effective therapy should always be guided by the most recent data regarding the pathogenic mechanisms, careful study of those mechanisms is crucial to advances in therapy [73,74]. There is evidence to suggest involvement of both humeral and cell-medicated autoimmune mechanisms in CIDP.

Since early evidence suggested an autoimmune pathogenesis for CIDP, early attempts at therapy included the use of glucocorticoids alone or in combination with plasmapheresis [12,53,66]. Immunosuppressive drugs such as methotrexate [75] and mycophenolate mofetil [76,77] have shown some promise. The age of biological therapy was introduced with intravenous immunoglobulin therapy [78] but monoclonal antibodies such as Retuximab and Natalizumab have also been tried in this condition with promise of potential benefit [79]. There is evidence that IVIG may work by down regulation of B-cell activating factor (BAFF) and, and perhaps other inflammatory cytokines [74]. It was documented that IVIG contained antibodies to BAFF and BAFF levels in CIDP serum were reduced by IVIG infusion [74].

FMS/CIDP overlap syndrome

FMS/CIDP clinical manifestations

Numerous presenting signs and symptoms are found in both CIDP and FMS populations, so many of those same symptoms would be expected to be present in patients with the composite condition of FMS/CIDP. In particular, fatigue, sleep disturbances and restless legs syndrome are common in both CIDP and FMS [1,51,69,71,80-82]. Additionally, Caro et al. [1] demonstrated paresthesia (76%), stocking hypaesthesia (hypoesthesia) (88%) and subjective weakness (90%) in their FMS study population, clinical symptoms which are also found in CIDP patients. Accordingly, many patients who are being treated for FMS may truly be misdiagnosed CIDP patients or may be experiencing a co-morbid overlap of CIDP with FMS (herein FMS/CIDP). Because the contemporary treatment options are very different in these two conditions, accurate identification and diagnosis is paramount to achieving good therapeutic outcomes.

FMS/CIDP diagnosis

At the present time, it seems most logical to make the diagnosis of the FMS aspect of FMS/CIDP using the validated criteria for the diagnosis of FMS 2010 ACR FDC (96% sensitivity) [30]. Similarly, to identify the CIDP component diagnosis in patients with FMS/CIDP

the recommendation would be for a neurologist to be involved in the process and to use the most sensitive validated criteria available for making the diagnosis of CIDP. According to the discussion above (CIDP Diagnosis) that would be the EFNS/PNS criteria (96% sensitivity) [69].

FMS/CIDP epidemiology

Lacking published formal epidemiology studies regarding this topic, one is free to speculate regarding what the answers might be, if the questions were to be formally studied. Based on the 2% prevalence (5,000,000 persons) of FMS in the United States general population [34,35], and the finding of Caro that 33% of FMS actually had FMS/CIDP [1] one can calculate that about 0.66% of the USA general population (1,650,000 persons) may actually have FMS/CIDP or CIDP misdiagnosed as FMS.

FMS/CIDP management

Once a patient is identified as having a convincing diagnosis of FMS/CIDP, it seems prudent that the clinician would apply the most effective contemporary therapy for the CIDP component. According to the medical literature, that intervention is currently a combination of glucocorticoid and a series of IVIG infusions [12,80]. In the future, the IVIG infusions could potentially be replaced by Retuximab infusions or by monoclonal antibodies strategically-specific for selected cytokines involved in the neurologic injury of CIDP [80]. It is less clear that the FMS component of FMS/CIDP should be treated as one would treat primary FMS.

The FMS/CIDP patients treated by Caro et al. seemed to resolve their FMS symptoms with IVIG infusions [1]. One view would be to hold direct therapy for the FMS in hopes that symptomatic improvement of the CIDP will be associated with improvement of the FMS component that can be relied upon as a sign of overall improvement. An alternate view would be that the clinician should provide more direct. though temporary treatment of the widespread pain and sleep dysfunction associated with the FMS component to reduce the severity of the symptoms and give the patient reason for compliance with the entire IVIG therapeutic program.

Summary

Regarding the FMS/CIDP overlap syndrome

Caro et al. have provided evidence to suggest that it is relatively common for CIDP and FMS to coexist [1]. In that regard, it is incumbent upon the clinician to recognize the FMS features and note that additional manifestations, such as weakness and hyporeflexia may forecast the presence of a destructive autoimmune neurologic process like CIDP in the same patient. A neurologist should be involved in the diagnosis of the CIDP component. When that overlap complex is found, the clinical manifestations of both syndromes may both respond to IVIG infusion therapy [1].

Acknowledgments and Disclosures

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