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Concise Report

A subset of fibromyalgia patients have findings suggestive of chronic inflammatory demyelinating polyneuropathy and appear to respond to IVIg

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Objectives. The aetiopathogenesis of the fibromyalgia syndrome (FMS) remains unknown. Recent reports, however, suggest that a subgroup of FMS subjects has an immune-mediated disease. Therefore, our primary objective was to study FMS subjects for evidence of an immune-mediated demyelinating polyneuropathy. Our secondary objective was to determine the effects of treating these FMS subjects with the immune modulator, intravenous immunoglobulin (IVIg).

Methods. Fifty-eight FMS subjects, 26 rheumatic non-FMS subjects and 52 non-rheumatic non-FMS subjects were studied. Subjective measures of paraesthesias, weakness, stocking hypaesthesia, pain, fatigue and stiffness were made. Objective measures of tenderness, proximal muscle strength and electrodiagnostic (EDX) evidence of polyneuropathy and demyelination were also made. Eleven other FMS subjects underwent sural nerve biopsy.

Results. Paraesthesias, subjective weakness and stocking hypaesthesia were more common in FMS than in rheumatic non-FMS ($P \leq 0.0001$). Proximal muscle strength was less in FMS than in rheumatic non-FMS ($P \leq 0.0001$). EDX demonstrated a distal demyelinating polyneuropathy, suggestive of chronic inflammatory demyelinating polyneuropathy (CIDP), in 33% of FMS subjects. No rheumatic non-FMS subject had polyneuropathy ($P = 0.005$), or demyelination ($P = 0.05$). Fifteen FMS/CIDP subjects were subsequently treated with IVIg (400 mg/kg each day for 5 days). Pain ($P = 0.01$), tenderness ($P = 0.001$) and strength ($P = 0.04$) improved significantly. Fatigue and stiffness trended towards improvement.

Conclusions. A significant subset of FMS subjects have clinical and EDX findings suggestive of CIDP. IVIg treatment shows promise in treating this subset. These observations have implications for better understanding and treating some FMS patients.

Key words: Fibromyalgia, IVIg, Chronic inflammatory demyelinating polyneuropathy.

Introduction

Clinical experience suggests the existence of a fibromyalgia syndrome (FMS) subgroup exhibiting features of immune dysregulation. Findings for this include Raynaud's phenomenon, sicca symptoms, livedo reticularis, the production of antinuclear and antipolymer antibodies, abnormalities in T-cell activation and CD4 : CD8 ratios, cytokine expression and cutaneous deposition of immunoreactants [1–11]. Since many FMS symptoms are neuropathic in nature we studied FMS, and non-FMS, patients for evidence of immune-mediated injury of the peripheral nervous system. We report here a surprisingly high prevalence of clinical and electrodiagnostic (EDX) abnormalities implying a demyelinating polyneuropathy, suggestive of chronic inflammatory demyelinating polyneuropathy (CIDP), in FMS. Furthermore, we report the amelioration of some FMS symptoms, in this subset, with intravenous immunoglobulin (IVIg), a known immune modulator.

Subjects and methods

Our FMS group was 58 consecutive rheumatic disease subjects (mean age 63 yrs, range 18–92 yrs; 53 females), meeting American College of Rheumatology FMS criteria [12]. Our rheumatic non-FMS group was 16 consecutive rheumatic disease patients (mean age 64 yrs, range 33–80 yrs; 11 males) who lacked FMS. Our non-rheumatic, non-FMS group was 52 subjects referred concurrently for EDX by other physicians. Ten other rheumatic non-FMS subjects (mean age 73 yrs, range 59–81 yrs; 7 males) also underwent comparison EDX examination. None of our EDX subjects had a medical, rheumatological or post-surgical condition that influenced EDX interpretation. The Northridge Hospital Institutional Review Board (IRB) approved this study. Written informed consent from all experimental subjects was obtained according to the Declaration of Helsinki.

Self-administered questionnaires assessed paraesthesias and subjective weakness. Stocking hypaesthesia was diagnosed by a Wartenberg pinwheel and 128 Hz tuning fork [13]. Proximal muscle strength was measured using modified Medical Research Council (MRC) [14] guidelines. Muscle groups were tested bilaterally: shoulder abductors, forearm flexors, hip flexors and knee flexors (total eight muscle groups). No attempt was made to isolate muscles more specifically, or to test distal extremity musculature. MRC results were converted to a 'strength score' for each subject.

EDX examinations consisted of EMG and nerve conduction studies (NCS) using a Neuro Diagnostic LBM machine. EMG studied right-sided extremities and associated paraspinal muscles. Bilateral NCS tested median, ulnar, peroneal, posterior tibial and sural nerves. A demyelinating polyneuropathy was defined as: two or more nerves, not including the median nerve, with conduction velocities 2 S.D., and often 3 S.D., below normal published values [15,16]. H-reflex, and F-wave measurements were included [17]. These EDX criteria most closely follow those suggested by the Inflammatory Neuropathy Cause and Treatment (INCAT) group [18], Saperstein *et al.* [19] and Rotta *et al.* [20]. No subject had another clinically apparent, congenital, nutritional, infectious or rheumatic disease (e.g. vasculitic) cause of their EDX findings. The prevalence of monoclonal gammopathies of undetermined significance (MGUS), as detected by immunofixation electrophoresis (IFE) did not differ significantly between FMS subjects (9%) and rheumatic non-FMS subjects (6%). Carpal tunnel syndrome

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TABLE 1. Clinical and EDX results in study populations

	FMS	Rheumatic non-FMS	Non-Rheumatic non-FMS	FMS *vs* rheumatic non-FMS *P*–value[a]	FMS *vs* non-rheumatic non-FMS *P*–value[a]
Total, *n*	58	16 clinical exams 10 EDX exams	52		
Mean age, yrs (range)	63 (18–92)	64 (33–80) clinical 73 (59–81) EDX			
Female, *n* (%)	53 (91)	5 (31) clinical 3 (33) EDX			
Ethnicity, *n* (%)	Caucasian: 37 (64) Hispanic: 20 (34) Black: 1 (2)	Caucasian: 11 (69) Hispanic: 4 (25) Asian: 1 (6)			
Paraesthesias, *n* (%)	39 (76)	3 (20)		<0.0001	
Subjective weakness, *n* (%)	46 (90)	2 (13)		<0.0001	
Stocking hypaesthesia, *n* (%)	51 (88)	0 (0)		<0.0001	
Proximal muscle strength score, (0–9) ± S.D.	7.6 ± 0.8	8.9 ± 0.2		<0.0001	
Polyneuropathy[b], n (%)	23 (47)	0 (0)	2 (5)	0.005	<0.0001
Demyelination[b], n (%)	16 (33)	0 (0)	2 (5)	0.05	0.003
LE non-dermatomal muscle denervation, n (%)	7 (15)	0 (0)	0 (0)	NS	0.02
CTS, n (%)	22 (45)	1 (10)	30 (68)	NS	0.04
CTS with demyelination, n (%)	19 (39)	1 (10)	29 (66)	NS	0.01

[a]Proximal muscle strength comparisons by Mann–Whitney (two–tailed). All other comparisons by Fisher's exact test (two-tailed). Rapid plasma reagin and serum vitamin B12 determinations were normal in all FMS and rheumatic non-FMS participants. [b]Not including CTS. LE, lower extremity; NS, not significant (P value > 0.05).

(CTS) was diagnosed if either median distal motor latency (measured to wave onset) ≥4.6 ms or median distal sensory latency ≥3.7 ms [15,16].

A CIDP-like illness was defined as: lower extremity stocking hypaesthesia, proximal muscle weakness in at least two extremities, and EDX evidence of a demyelinating polyneuropathy.

To further assess the nature of any neuropathic injury in FMS, 11 subsequent FMS subjects (9 females; mean age 61 yrs, range 42–81 yrs), who satisfied criteria for inclusion in the current study, underwent sural nerve biopsy. Three subjects had diagnosed conditions that could have influenced their biopsy results (one type 2 diabetes mellitus, two RA). All of the subjects had abnormal EDX examinations suggesting a demyelinating sensorimotor polyneuropathy. The same neuropathologist examined all biopsy specimens for morphometry, single fibre teasing and ultrastructural analysis (Neuromuscular Disease Laboratory, David Geffen School of Medicine at UCLA, Los Angeles, CA, USA).

Open-label IVIg (ZLB Inc., Burbank, CA, USA) treatment was provided to 15 FMS patients exhibiting demyelinating polyneuropathy, normal cardiovascular, renal and hepatic status, detectable serum IgA and vascular accessibility. To limit IVIg side-effects, subjects received a single i.m. injection of methylprednisolone acetate 40 mg, 2–7 days prior to IVIg infusion [21] and acetaminophen 1000 mg and loratidine 10 mg, as needed, at the time of infusion. IVIg was given at 400 mg/kg each day for 5 days (i.e. total of 2 gm/kg) [22].

Complaints of pain, fatigue, morning stiffness, objective tenderness and proximal strength were recorded pre-IVIG and 2–4 weeks post-infusion. Pain was rated on a 0–10 scale (10 being maximal). Fatigue was recorded as present or not, and morning stiffness was recorded in minutes (480 min maximal). One author (X.J.C.) assigned a tenderness score, ranging from 0 to 3 (3 being maximal tenderness).

Results

Clinical and EDX examination results are listed in Table 1. No subject had EDX evidence of any entrapment neuropathy other than CTS, or signs of a metabolic myopathy or myositis. Sural nerve biopsy results from 11 subsequent FMS subjects satisfying criteria for inclusion in the current study are shown in Table 2. Two subjects showed minor degenerative axonal changes (one had RA, the other type 2 diabetes mellitus). Two of 11 biopsies also showed some large myelinated fibre loss. None of the 11 biopsies showed amyloid deposits, vasculitis or nerve inflammatory infiltrates.

TABLE 2. Summary of myelinated fibre findings in sural nerve biopsies from 11 FMS subjects

Histological finding	Percent
Increased large/small fibre ratio[a]	78
Myelin thinning	64
Reduced number of fibres	55
Segmental demyelination	36
Remyelination	27
Regenerative clusters	27
Onion bulb formation	9

[a]Based on nine specimens.

TABLE 3. Clinical outcome of IVIg treatment in 15 FMS patients with a CIDP-like component to their clinical picture

Clinical marker	Pre-infusion	Post-infusion	*P*-value[a]
Pain, (0–10) ± S.D.	6.8 ± 2.3	4.4 ± 2.0	0.01
Fatigue, (present)	9	6	NS
Stiffness, (0–480 min) ± S.D.	216 ± 211	192 ± 226	NS
Tenderness score, (0–3) ± S.D.	1.8 ± 0.7	0.8 ± 0.6	0.001
Proximal muscle strength score[b], (0–9) ± S.D. (only 14 subjects)	7.8 ± 0.8	8.3 ± 0.7	0.04

[a]Wilcoxon signed-rank test (two-tailed) except for fatigue, which used Fisher's exact test (two-tailed). [b]Numerically converted Modified British Research Council Scale (13). NS, P-value > 0.05.

IVIg treatment results are given in Table 3. Mean proximal muscle strength scores are given in Table 3 for 14 of the 15 patients because post-IVIg strength was inadvertently not recorded in one. Three of nine patients had loss of their fatigue post-infusion. Nevertheless, this change in fatigue, as a group, did not reach statistical significance in our small population. No significant adverse effects of IVIg were seen.

Discussion

The neuropathic nature of the painful symptoms commonly seen in FMS suggested to us the possibility of a coexisting CIDP-like illness. For example, 76% of our FMS subjects claimed paraesthesias, a feature commonly associated with CIDP [23–25]. Only 20% of our rheumatic non-FMS subjects had paraesthesias ($P < 0.0001$). This high prevalence of paraesthesias in our FMS

subjects compares well with that of Simms and Goldenberg [26] who found that 84% of 161 FMS patients had such complaints. Martinez-Lavin *et al.* [27] also noted that 95% of their FMS patients described dysaesthetic sensory disturbances, compared with 30% of their RA patients ($P < 0.0001$).

We found a high prevalence of stocking distribution hypaesthesia in our FMS group (88%) but none in our rheumatic non-FMS group ($P < 0.0001$). Numbness and paraesthesias, often involving all four extremities, are reported in 85.5% of adult CIDP patients in Simmons and Albers' review of CIDP [23], and 64–89% of patients in Hahn *et al.*'s review [25]. So far as we are aware, the finding of stocking distribution hypaesthesia, as a physical finding in FMS, has not been previously described.

Though pain remains the *sine qua non* of FMS, it is not often thought of as a component of CIDP. Nevertheless, Gorson *et al.* [28] found that 42% of their CIDP patients had prominent pain. Likewise, Hahn *et al.* [25] found that between 8% and 20% of CIDP patients had pain. Devor [29] has reviewed the role of injured, large myelinated nerve fibres, such as those classically affected in CIDP, in peripheral pain production. Scadding and Koltzenburg [30] point out that sensory lesions, in general and particularly those of unmyelinated nociceptors (often cutaneous) probably participate in most peripheral neuropathic states. Unmyelinated nerve fibre lesions have recently been described in CIDP [31].

We found that 90% of our FMS subjects had complaints of weakness, compared with only 13% of rheumatic non-FMS subjects ($P < 0.0001$). Furthermore, FMS patients were significantly weaker on examination than rheumatic non-FMS subjects ($P < 0.0001$). Muscle weakness has been reported in FMS [32, 33], and is common in CIDP [23, 28].

EDX is a relatively simple, readily available tool, which can be a sensitive, though not perfect, aid in the diagnosis of neuropathic illnesses. Simms and Goldenberg [26] reported minimal EDX abnormalities, mostly CTS, in their FMS subjects. Their study, however, was limited to a retrospective chart review of EDX findings, and was not intended to focus on the prospective EDX evaluation that we, and others, have carried out [34, 35]. By using a systematic EDX approach we were able to identify a polyneuropathy in 47% of our 58 FMS subjects, while only 5% of the 52 non-rheumatic, non-FMS subjects had such findings ($P < 0.0001$). Seventy percent of our FMS subjects with a polyneuropathy also had EDX evidence of demyelination, usually marked by conduction slowing, dispersion phenomena and/or abnormal H-wave reflexes [15–17]. The disadvantage of EDX is that it remains implicative, rather than discriminative, in the diagnosis of demyelination and CIDP.

Most agree that nerve biopsy in CIDP provides the single most definitive evidence for this diagnosis, both through the exclusion of other, sometimes confusing, neuropathic disorders and through the identification of subtle changes confirming the presence of a demyelinating condition [36]. It was impractical, however, to obtain such invasive testing on all of the FMS subjects in this clinical study, and unethical to consider such biopsies in our comparison groups. We did, however, perform sural nerve biopsies on 11 subsequent FMS subjects who would have fulfilled clinical and EDX criteria for inclusion in this study. While uncontrolled, this series of biopsies (Table 2) failed to provide any other obvious explanation for these patients' EDX and clinical findings (e.g. no evidence of amyloidosis or vasculitis). Furthermore, a majority of them showed signs suggestive of myelin injury, including segmental de- and remyelination, and/or apparent, small myelinated nerve fibre drop out. Although ageing itself can cause some myelinated fibre loss in sural nerve biopsies, age-related changes alone seem an unlikely explanation for our subjects' findings since age-related sural nerve fibre loss most prominently affects large myelinated fibres [37]. The lack of cellular infiltrate in our subjects' sural nerve tissue is not unexpected since the presence of inflammatory cells involving sural nerve biopsies in CIDP is considered rare [37].

In this study, we took our clinical findings to their logical conclusion by treating 15 selected FMS subjects with IVIg, a biologic agent known to benefit CIDP [38]. A large percentage of this select FMS subset experienced significant short-term benefits from IVIg treatment, at least in terms of pain, tenderness and strength. Although it might be argued that our patients' improvement was in some way tied to their infusion-related premedication with methylprednisolone, this seems unlikely. This medication was provided because of our concern for safety during this novel treatment programme [21]. There is no real evidence that low-dose steroids benefit FMS, and some published evidence that it does not [39]. Of course, we cannot exclude, on the basis of this preliminary study, the possibility that some other unrecognized clinical variable, such as age, gender or even a placebo effect might have significantly affected these subjects' improvement with IVIg. A larger, blinded and placebo-controlled trial of IVIg in this subset of FMS subjects ought to better answer such questions.

It should also be emphasized that despite our FMS/CIDP patients' relatively innocuous experience, IVIg is not altogether benign. The side-effects of IVIg may include headache, fever, myalgias, tachycardia, renal tubular necrosis, hyperviscosity (with potential for stroke and myocardial infarction), anaphylaxis (particularly in IgA-deficient individuals), haemolysis, hepatic injury, rashes, cutaneous vasculitis and thromboembolic events [40].

Finally, it is worth noting that we did not set out in this pilot study to provide proof of CIDP in FMS. In fact, research criteria for the diagnosis of CIDP can be rather restrictive, so instead, we attempted to merely ascertain the presence, and demyelinating nature, of the neuropathic process seen in a subset of FMS subjects. Nevertheless, we have been influenced by our FMS subjects' clinical and laboratory findings, their apparent response to IVIg, and statements by leaders in the field, such as Latov [41], who notes that '... most acquired demyelinating neuropathies of otherwise unknown etiology are considered to be a form of CIDP'. For all of these reasons, we classified our FMS patients as having a disorder suggestive of CIDP.

In summary and conclusion, we have described a subset of FMS patients with findings suggestive of CIDP, a disorder known to be immune mediated. This FMS/CIDP subset may constitute a significant portion of the overall, non-homogeneous family of FMS. Furthermore, it is readily identifiable, and may be responsive to IVIg, a known immune modulator. This subset of FMS appears worthy of further study, and may afford medical scientists a new avenue of understanding and therapeutics in this enigmatic disorder.

Rheumatology key messages

- Subset identification in FMS appears worthwhile.
- CIDP-like symptoms define a significant subset in FMS.
- This CIDP subset in FMS may respond to IVIg treatment.

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