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Original Article

Neural and muscular dysfunction in fibromyalgia

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ABSTRACT
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Objectives: Our aim was to assess peripheral neural and muscular dysfunction in patients with fibromyalgia syndrome (FMS) by interrelating different electrophysiologic and histopathologic studies, in a trial to further elucidate the pathophysiology of fatigue in FMS.
Methods: Thirty FMS patients and ten controls were enrolled in the study. To test for muscle fatigue, muscle fiber conduction velocity (MFCV) and quantitative surface EMG analysis were performed before and after sustained contraction. Muscle biopsies were examined by light and electron microscopy.
Results: Electrodiagnostic studies revealed pathological fatigue response in patients compared to controls. Patients showed statistically significant lower MFCV ($P < 0.0001$) and higher percent drop in MFCV following sustained contraction ($P < 0.001$).

Light microscopy examination of patients' muscle biopsies revealed a significantly higher percentage of fiber size variability, increased central nucleation, increased glycogen and higher percent increase in fiber type I.

Electron microscopy revealed different abnormalities. The aggregation of bizarrely-shaped mitochondria was the most remarkable finding in all patients, but in none of the controls.
Conclusion: There is definite evidence of neural and muscular interconnected dysfunction. The development of fatigue in FMS is significantly influenced by fiber type composition of the skeletal muscle and disrupted muscle mitochondria.
Key words: Fibromyalgia, pathophysiology, sympathetic skin response, muscle biopsy, muscle fiber conduction velocity

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Introduction

Fibromyalgia syndrome (FMS) is not a specific disease but rather a syndrome of several medically unexplained symptoms such as chronic pain, chronic fatigue, sleep disturbances and mood disorders [1, 2]. Over the years, several pathogenic mechanisms for the condition have been postulated but the exact pathogenesis still remains a mystery [3].

Fatigue, along with frequently reported muscle weakness and stiffness, are of great concern to FMS patients. The musculoskeletal, neuroendocrine, and central nervous systems appear to play major roles in the pathogenesis of fatigue [4−6]. To obtain more insight into the causes of the excessive fatigue seen in patients with FMS, it is important to first determine the sites involved in the fatigue process and whether it is impaired motor drive from the nervous system or impaired muscular ability to generate force.

Electrophysiologic studies are one of the best tools used to detect muscle fatigue. However, due to the high (theoretically unlimited) temporal resolution of electrophysiological measurements, surface electromyography (EMG) has long been used in the assessment of central nervous system activation of

muscles to evaluate what is referred to as central fatigue. Actually, invasive EMG (needle electrodes) and surface EMG (surface electrodes) give complementary information: the invasive EMG shows the dropout of fibers while the surface EMG shows the physiological adaptation of surviving motor units [7].

Fatigue is also accompanied by changes in muscle fiber electrical activity [8]. Muscle fiber conduction velocity (MFCV) is another convenient means to study muscle behavior under fatigue. MFCV is the speed of the depolarization wave along the muscle fiber membrane, or sarcolemma. It is frequently used to study muscle function in neuromuscular diseases [9].

Aberrations in autonomic nervous system (ANS) functioning are often observed among patients with fibromyalgia. ANS abnormalities may contribute to enhanced pain, constant fatigue and other symptoms associated with low blood pressure via the alteration of physiologic responses required for effective stress management [10]. Sympathetic skin response (SSR) is a simple noninvasive test for assessing sudomotor function in any autonomic dysfunction [11].

Other aspects of research into fibromyalgia muscle function include the search for evidence of more objective findings. Over the years, there has been a variety of muscle biopsy studies, but with conflicting results. Some earlier studies found significant morphological abnormalities; others did not [10, 12].

Although fatigue, muscle weakness and autonomic dysregulation have previously been studied separately, we have yet to find a study on the interrelation between different neurophysiological studies and the findings of muscle biopsy.

It is expected that advances in understanding the pathophysiology of fibromyalgia will contribute to the development and validation of efficacious pharmacologic and behavioral treatments for these disorders.

This study was designed to assess peripheral neural and muscular dysfunction in patients with FMS by interrelating different electrophysiologic and histopathologic studies, in a trial to further elucidate the pathophysiology of fatigue in FMS.

Methods

1. Study participants

This study was conducted on thirty patients with FMS fulfilling the 1990 ACR criteria for diagnosis of FM [13]. Participants were consecutively recruited from Physical Medicine, Rheumatology and Neurology outpatient clinics. A control group of ten apparently healthy volunteers of comparable age and gender was also included. Patients were 27 females and 3 males with a female to male ratio of 9:1. Their ages ranged from 18 to 60 years with a mean age of 36.4 ± 12 years. The control group comprised 9 females and 1 male with a mean age of 37 ± 14.15 years.

The study protocol was approved by the Ethics Committee of Faculty of Medicine, Ain Shams University , and informed consent was obtained from each participating subject.

All patients and controls underwent the following:

A. **Full medical history taking:** Pain, fatigue and disability were assessed using visual analogue scales (VAS) [14]
B. **Clinical examination** including number of tender points [15]
C. **Routine laboratory tests**
D. **Electrodiagnostic tests** (using a Dantec Counterpoint EMG/EP system) including:
   1. Motor and sensory nerve conduction studies for both median, ulnar and tibial nerves
   2. Sympathetic skin response (SSR) of both median nerves [11]. The mean values of peak-to-peak amplitude, latencies and duration were then calculated for both sides.
   3. Conventional basic needle EMG
   4. ***Neurophysiologic tests for muscle fatigue***
      - Muscle fiber conduction velocity (MFCV) using a cross-correlation technique [16]. Two bipolar surface electrodes are placed in a linear array, parallel to the muscle fibers, nearly halfway between the endplate zone and the distal tendon. The MFCV is calculated from the latency shift between the two EMG signals. Other EMG parameters are also measured. MFCV was calculated twice to compare the values before and after one minute of sustained contraction. The test was performed on both sides, and then their average value was calculated.
      - Quantitative surface EMG analysis of interference pattern was performed [8]. Bilateral biceps brachii muscles were tested with maximal and 70% submaximal contractions. Data was recorded before and after one minute of sustained contraction to quantitate the changes in the recruitment pattern of the fatigued muscle, at a frequency window of 1.4 KHz. In the time domain, we used the root mean square, mean rectified voltage and mean amplitude. In the frequency domain, we used the mean and median power frequency.
E. ***Muscle biopsy***: Open biopsies of tender points in the muscle (one patient from the quadriceps and the others from the deltoid muscle) and from corresponding sites in the controls were obtained. Local anesthesia was used to obtain a specimen of 0.5×1.5 cm. The specimen was then divided into three parts to be prepared for examination by light and electron microscopy. The first part of

the specimen was used for enzyme histochemical staining by NADH-Tr and ATPase enzyme stains [17]. Myofibril adenosine triphosphatase (ATPase) was used to differentiate muscle fiber types. Nicotinamide adenine dinucleotide tetrazolium reductase (NADH-Tr) was used for staining intermyofibrillar material (mitochondria and sarcoplasmic reticulum). The second part of the specimen was preserved in formalin to be examined regularly with haematoxylin and eosin (H&E) stain (T.S. & L.S.). The third part of the specimen was immersed immediately in 5% gluteraldehyde, buffered with 0.1 M sodium cocodylate at pH 7.3. The specimen was left for four hours at a temperature of 4°C to be processed for conventional transmission electron microscopy (Phillips 400T) at 60 KV accelerating voltage.

Owing to the importance of the mitochondrial changes at the cellular level in the etiology of fatigue, patients who had positive mitochondrial morphological changes were given a score: +1, +2 or +3 referring to the degree of existing pathology, with +1 being the least in number and pleomorphism and +3 being the maximum in number and pleomorphism. Other microscopic findings were simply reported as positive or negative.

F. Statistical analysis for the collected data was followed by correlation between clinical, histopathological and electrophysiological findings in which:
- The X^2 test (chi-square) was performed for testing the association between parameters.
- The ANOVA (F) test was used for testing the difference in certain parameters between groups.
- The Student t-test was used for testing the difference in mean values between two groups.
- P = probability
- Spearman's rank correlation coefficient (r) was used to measure the association between variables.

Program used: SPSS 7.5 for Windows (Statistical Package for Social Science).

Results

The patients' clinical data is shown in Table 1.

All laboratory data for patients and controls is within the average reference range.

Electrodiagnostic results

1. Nerve conduction studies

Nerve conduction studies showed entrapment neuropathies in 14 patients. Among these patients, five (16.7%) had CTS, seven (23.3%) had ulnar entrapment, and eight (26.7%) had tarsal tunnel syndrome.

2. Sympathetic skin response (SSR)

SSR revealed significant delayed latencies in patients compared to controls (patients: 1.23 ± 0.41, controls: 0.86 ± 0.27; $P < 0.05$). There was no statistically significant difference between patients and controls regarding the rest of the data ($P > 0.05$).

3. Conventional basic needle EMG

All examined muscles showed silence at rest and average motor unit analysis on volition (parameter mean ± SD in patients vs controls are as follows: duration in ms: 7.82 ± 1.62 vs 7.20 ± 1.53; amplitude in uV: 314.63 ± 93.75 vs 249.00 ± 89.28 and % polyphasicity: 7.82 ± 1.62 vs 4.30 ± 2.58). There was no significant statistical difference between patients and controls using Student's T test ($P < 0.060$, 0.294, and 0.953 for the previously mentioned parameters, respectively).

4. Testing muscle fatigue

- MFCV revealed that patients had definite pathological fatigue response compared to controls. To represent the quantity of fatigue, the percent drop in MFCV was calculated. Patients showed statistically significant higher percent drop in MFCV (Table 2).
- Quantitative surface EMG analysis of interference pattern at maximum and submaximal contraction

Table 1. Parametric clinical data on patients.

Parameters	Minimum	Maximum	Mean ± S.D.
VAS for pain	5.00	10.00	7.53 ± 1.14
VAS for fatigue	4.00	9.00	7.43 ± 1.48
VAS for disability	6.00	9.00	7.60 ± 1.16
MADRS	17.00	53.00	36.50 ± 9.00
Number of tender points	12.00	18.00	14.97 ± 1.94
Disease duration (years)	3 months	20 years	4.53 ± 4.48
Morning stiffness duration (minutes)	5 minutes	45.00	9.83 ± 13.86

VAS, Visual analogue scale.
MADRS, Montgomery-Åsberg Depression Rating Scale.

Table 2. Muscle fiber conduction velocity (MFCV) in patients and controls.

MFCV m/s	Control Mean ± SD	Patients Mean ± SD	*t*	*P*	Sig.
Velocity: before	7.77 ± 2.05	4.81 ± 1.27	5.44	< 0.0001	HS
Velocity: after	7.70 ± 2.01	3.63 ± 1.45	6.96	< 0.0001	HS
Percent drop $\frac{B-A}{B}\times 100$	0.91 ± 1.38	25.82 ± 22.03	−3.542	0.001	HS

Table 3. Surface EMG analysis before and after sustained submaximal contraction.

Quantitative EMG analysis		Control Mean ± SD	Patients Mean ± SD	*t*	*P*	Sig.
RMS uV	Before	65.13 ± 17.86	118.01 ± 46.37	−3.496	0.001	HS
	After	48.79 ± 20.68	109.56 ± 86.37	−2.187	0.035	S
MRV uV	Before	52.99 ± 15.48	89.27 ± 35.76	−3.092	0.004	S
	After	43.23 ± 17.38	74.54 ± 29.19	−3.190	0.003	S
MNF Hz	Before	78.84 ± 5.75	83.22 ± 27.28	−0.501	0.620	NS
	After	85.92 ± 6.66	81.18 ± 18.08	0.804	0.427	NS
MDF Hz	Before	58.43 ± 4.90	64.60 ± 21.16	−0.906	0.371	NS
	After	51.63 ± 10.11	62.01 ± 13.21	−2.266	0.029	S
Mn. Amp uV	Before	212.85 ± 83.96	307.45 ± 85.56	−3.041	0.004	S
	After	157.90 ± 65.18	265.12 ± 71.51	−4.191	< 0.0001	HS

RMS, root mean square; MRV, mean rectified voltage; Mn. Amp., mean amplitude; MNF, mean frequency; MDN, median frequency.

Table 4. Surface EMG analysis before and after sustained maximum contraction.

Quantitative EMG analysis		Control Mean ± SD	Patients Mean ± SD	*t*	*P*	Sig.
RMS uV	Before	195.42 ± 91.20	297.08 ± 99.74	−2.84	0.007	S
	After	135.54 ± 07.36	156.86 ± 55.15	−0.82	0.416	NS
MRV uV	Before	148.75 ± 69.09	236.93 ± 79.83	−3.11	0.003	S
	After	99.66 ± 68.87	123.62 ± 41.59	−1.32	0.192	NS
MNF Hz	Before	84.31 ± 8.98	85.07 ± 16.84	−0.13	0.893	NS
	After	81.62 ± 11.70	77.01 ± 14.77	0.89	0.376	NS
MDF Hz	Before	69.80 ± 6.65	69.84 ± 12.12	−0.009	0.993	NS
	After	61.30 ± 8.19	61.34 ± 11.05	−0.010	0.992	NS
Mn. Amp uV	Before	397.25 ± 90.86	600.80 ± 177.61	−3.45	0.001	HS
	After	256.60 ± 60.36	375.30 ± 96.84	−3.63	0.001	HS

RMS, root mean square; MRV, mean rectified voltage; MNF, mean frequency; MDF, median frequency; Mn. Amp., mean amplitude.

revealed significant lowering in different parameters in patients compared to controls (Tables 3 & 4).

Muscle biopsy

- H&E stained sections showed a significantly higher percentage of fiber size variability in patients compared to controls (detected in 22 patients and 3 controls, $P = 0.02$) and increased central nucleation (18 patients and 1 control, $P = 0.009$) (Figure 1).
- MT staining showed a highly significant increase in collagen content in patients (increase in 17 patients, $P = 0.001$). None of the patients or controls had fiber splitting.

- There were highly significant statistical differences between patients and controls in terms of fiber typing in the NADH and ATPase staining of the muscle biopsy ($P < 0.001$). Patients showed a higher percentage of increased type 1 among the fiber types (Table 5; Figure 2).
- Electron microscopy (EM) findings (Table 6): Aggregates of bizarrely-shaped (pleomorphic) mitochondria were observed in 100% of the patients but in none of the controls (Figure 3).

Correlation between the significant positive data of the patients

There was a statistically significant difference, using the chi-square test (χ^2), between mitochondrial

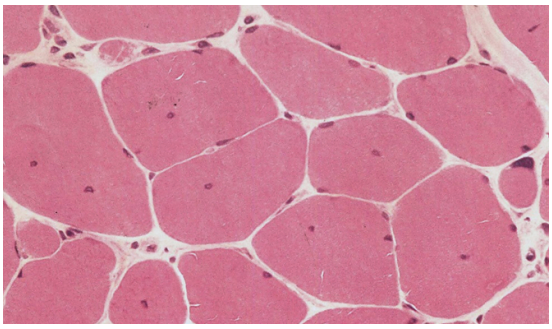

Figure 1. ↑ Central nucleation and fiber size variability in T.S. (Transverse Section).

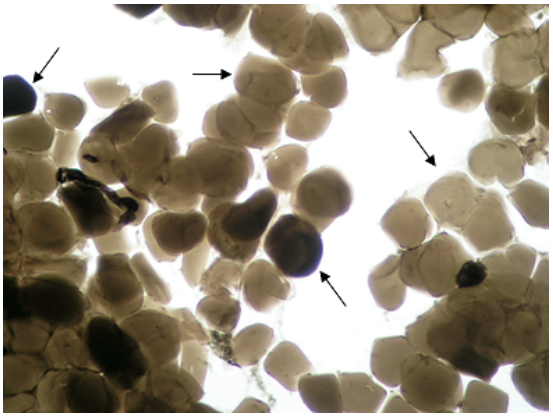

Figure 2. ↑↑ Type I (light brown) and type II (dark brown) by ATPase staining for the T.S. of the muscle fiber (×20).

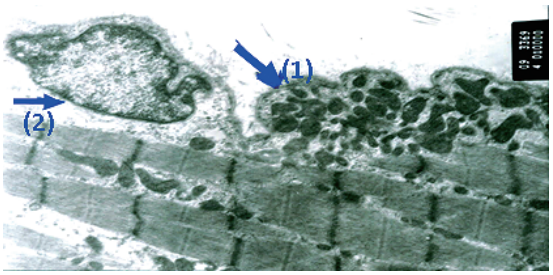

Figure 3. Subsarcolemmal aggregates of pleomorphic mitochondria (1) and vesicular nucleus with smooth contour (2) (Negative amplification 10000).

Table 5. Fiber typing in NADH and ATPase staining of muscle biopsy in patients and controls.

Fiber typing		Controls (10)		Patients (30)		χ^2	*P*	Sig.
		N	%	N	%			
NADH	↑↑ type I	2	20.0	24	80.0	*	0.001	HS
	type I=II	8	80.0	6	20.0			
ATPase	↑↑ type I	2	20.0	24	80.0	*	0.001	HS
	type I=II	8	80.0	6	20.0			

Table 6. Comparison between patients and controls in percentage (frequency) of EM findings.

EM data	Controls (10)		Patients (30)		*P*	Sig.
	N	%	N	%		
Increased fatty infiltration	4	40.0	22	73.3	0.12	NS
Bizarrely-shaped mitochondria	0	—	30	100.0	< 0.0001	HS
Sarcolemmal focal discontinuity	0	—	19	63.3	0.001	HS
Vesicular nucleus with smooth contour	0	—	20	66.7	0.0004	HS
Blood vessel abnormality	0	—	17	56.7	0.002	S
Focal loss of myofilaments	3	30.0	26	86.7	0.002	S
Increased lipofuscin	1	10.0	21	70.0	0.002	S
Sarcoplasmic disorganization	0	—	14	46.7	0.007	S

Table 7. Comparison between degree of mitochondrial pathology and fiber type.

		Fiber typing (ATPase)	
		↑↑ type I (24)	type I=II (6)
Bizarrely-shaped mitochondria	+	7	—
		29.2%	—
	++	11	—
		45.8%	—
	+++	6	6
		25.0%	100.0%
	Total	24	6
		100.0%	100.0%
$\chi^2 = 11.250$ $P = 0.004$ **S**			

ATPase, adenosine triphosphatase.

pathology grades and fiber typing by ATPase ($P<0.05$) where all patients with an equal percentage of both muscle fiber types (type I = II) had the most severely disrupted mitochondria while patients with type I fiber predominance had variant degrees of mitochondrial disruption (Table 7)

There was no statistically significant difference between different grades of bizarrely-shaped mitochondria in terms of the mean MFCV, mean percent drop in MFCV, VAS of pain, fatigue, disability and duration of complaint using the ANOVA test ($P > 0.05$) (Table 7).

Patients with an equal percentage of both muscle fiber types showed a statistically significant higher mean percent drop in the mean and median frequency compared to those with fiber type I predominance at submaximal contraction ($P < 0.05$).

Discussion

FM encompasses many symptoms, including fatigue, sleep disturbances, psychological and cognitive alterations, headache, migraine, variable bowel habits; diffuse abdominal pain, and urinary frequency [18, 19].

Histopathological changes in the muscle, as well as altered sympathetic nervous system responses have previously been reported. It is not clear yet whether these reported abnormalities are important factors of the reduced performance and excessive fatigue or in the pathogenesis of fibromyalgia itself [20].

Nerve conduction studies showed a high incidence of entrapment neuropathies among our patients (14 cases). This data is nearly similar to that reported by Ersoz [21], who added that the findings in his study indicate common focal neuropathies in FMS patients. He suggested that the etiology of such entrapments is most likely multifactorial.

Aberrations in autonomic nervous system (ANS) functioning are often observed among patients with fibromyalgia [22, 23]. Difficulty in maintaining blood pressure levels may contribute directly to some of the unpleasant symptoms frequently associated with fibromyalgia, such as fatigue and dizziness [10].

The bilateral statistically significant delayed distal latencies of the SSR in our patients, with the absence of correlation between SSR latencies and the distal motor and sensory latencies of both median nerves, suggests possible sudomotor sympathetic dysfunction in patients with FM. Our results simulate those of Ulas et al. [24].

In various neuromuscular disorders, MFCV is abnormal [25]. To date, no published studies have worked on the MFCV item in FM patients, although fibromyalgia is distinguished by fatigue. In our study, there was a statistically high significant difference between patients and controls in the mean values of MFCV before and after sustained contraction.

Our results are following the previous results [26] as most of our patients have type I predominance while the controls have a higher percent of type II fibers (fast conducting). However, sustained contraction of the biceps for one minute caused evident fatigue in patients but not controls.

Proceeding with our electrodiagnostic fatigue testing, we performed quantitative analysis for the interference pattern to assess amplitude and frequency changes in the power spectrum. Surface EMG (at submaximal and maximal contraction levels) is a convenient means to study the muscle behavior under fatigue, as it previously confirmed changes in either the time or the frequency domains [27], yet we noticed that the variability of the amplitude and frequency parameters was clearly larger than that of the MFCV estimation and the latter was obviously superior in detecting pathology.

In an attempt to further discover the mystery of muscle in fibromyalgia, we moved on to the muscle biopsy procedure. Numerous biopsy studies in FMS have demonstrated histological changes as moth-eaten fibers, ragged red fibers and abnormal mitochondria [26, 28−33].

Our patients showed a higher percentage of fiber atrophy, fibrosis, vacuoles, increased adipose tissue in the muscle, fiber size variability and increased central nucleation compared to the controls, but a statistically significant level was reached only in terms of fiber size variability and increased central nucleation. Increased fiber size variation and number of central nuclei are non-specific findings, and may be seen in most muscle diseases, in prolonged neuropathic diseases, or in any cause of fiber atrophy. Mitochondrial proliferation may be a compensatory phenomenon in disorders or pathophysiological states affecting oxidative metabolism. They appear to be related to insufficient blood supply [26].

In our study, most of the patients (56.7%) showed higher collagen content by Masson trichrome staining

of the muscle biopsy. These results are similar to those of Tuzlukov et al. [34] but contradictory to Gronemann et al. [35] who concluded that fibromyalgia patients had a significantly lower amount of intramuscular collagen. This variance could be explained by the different techniques and sites of the biopsy, and the higher mean disease duration of their patients compared to ours.

However, recent biopsy studies have found increased levels of collagen and inflammatory mediators in the fascia of fibromyalgia patients. This paper proposes that the dysfunction and inflammation of intramuscular connective tissue, or fascia, leads to the central sensitization seen in fibromyalgia [36].

Shifting to another cardinal point, the patients in this study showed a significantly higher percent of increased type I among the fiber types while the controls showed equal frequencies of the two types. This outcome agrees with several studies [26, 29, 37] that reported type II muscle fiber atrophy, but disagrees with Sprott et al. [38]. This variability in the results could be due to the better state of their patients as they selected only early FM patients.

Moving to a complementary analysis in our study, electron microscopy results were promising. The aggregation of bizarrely-shaped mitochondria was the most remarkable detection, as all the patients and none of the controls had such a finding. We also found that the highest percentage of patients (40%) had the maximum degree of mitochondrial pathology (+3). This data coincides with Sprott et al. [38], who stated that more patients presented with bizarrely-shaped mitochondria, sarcoplasmic disorganization, increased fatty infiltration and increased lipofuscin compared to the controls. We noticed endothelial hypertrophy in 66.7% of the patients. Bengtsson [26] mentioned in his study that the endothelial thickness found in the blood vessels of fibromyalgia patients is either caused by or is the cause of localized hypoxia. These findings suggest that the regulation of microcirculation is disturbed in fibromyalgia in a way that might lead to sensitization of the intramuscular nociceptors. In FMS patients, when the muscle is not relaxed between contractions, the microcirculation of the muscle might be affected, leading to a state of central sensitization. Central sensitization is defined as an increased response to stimulation that is mediated by the amplification of signaling in the central nervous system. Importantly, once central sensitization has occurred, only minimal nociceptive input is required to maintain the sensitized state and clinical pain [39].

In FMS patients, changes in the muscles, such as mitochondrial changes, a change in the microcirculation and/or a change in muscle metabolism, might sensitize muscle nociceptors and thereby cause pain, fatigue and muscle weakness.

One of the mysterious points to us in the beginning was why patients show fatigue in the first place despite having predominant type I fibers (fatigue resistant). In general, short-duration tasks depend on preexisting stores of ATP and creatine phosphate. Tasks of longer duration are driven either by the process of anaerobic glycolysis (done by fast glycolytic type II fibers, which are inadequate in FM patients), or by the oxidative pathways in the mitochondria (done by slow oxidative type I fibers using circulating fatty acids, or intramuscular lipid stores as fuel) [40]. So, by proving a definite mitochondrial pathology in our study, it is clear why patients are fatigued and why the lipid droplets (not being used for fuel) are increased within the muscle fibers.

On the other hand, we noticed that the patients with predominant equal fiber type (I = II) (6 in number) all had grade 3+ mitochondrial pathology, while patients with type I fiber predominance (24 in number) had varying degrees of mitochondrial disruption. Bearing in mind that type II fibers originally have less abundant mitochondria than type I, when muscles with predominant fibers type I = II have a pathology in the mitochondria there is no wide scope to compensate it. On the other hand, muscles with type I fiber predominance have a better chance for compensation by the higher number of available mitochondria.

Abdullah et al. (3) presented the case of a patient in whom the symptoms of fibromyalgia were related to an underlying mitochondrial disorder. Treatment of the mitochondrial disorder resulted in the resolution of symptoms. This case suggests the possible role of mitochondrial disease in the pathogenesis of the symptom complex of fibromyalgia, whereby not only is the underlying defect identified at the molecular and genomic level, but with appropriate therapy, significant symptomatic improvement is also noted.

Finally, we found no correlation between MFCV, bizarre mitochondria, the fiber types and any of the clinical symptoms or scores of the patients. The lack of objective clinical score for FMS, and the complete dependence of these scores on the patients' subjective feelings, may explain these unexpected results. It's well known that fibromyalgia patients have definitely proven exaggerated pain and fatigue sensations that may be far beyond the actual materialistic proven results. The electrophysiological and histopathological results are unbiased objective findings, and are more reliable to count on; hence they may not correlate with the subjective clinical data outcome.

Conclusion:

Fatigue in FMS patients has a demonstrable pathophysiological basis and does not represent somatization. It is significantly influenced by fiber type composition of the skeletal muscle and disrupted muscle mitochondria.

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