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Original Investigation

Ischemia-hyperpnea test is useful to detect patients with fibromyalgia syndrome

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Abstract

Objective: To demonstrate the prevalence of neuromuscular hyperexcitability in Fibromyalgia Syndrome (FMS) by electromyography ischaemia-hyperpnea test (IHT) and its correlation with clinical and clinimetric parameters.

Material and Methods: One hundred and forty-five FMS patients underwent IHT to evaluate neuromuscular hyperexcitability and were evaluated for pain (numeric Rating Scale and Regional Pain Scale), tenderness (tender points), disability [Fibromyalgia Impact Questionnaire (FIQ), Health Assessment Questionnaire (HAQ)], quality of life (QOL) [Short Form 36 (SF36)], mood [Hospital Anxiety and Depression Scale (HADS)], sleep [numeric rating scale (NRS)], and fatigue [Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT)].

Results: Of the 145 patients, 95 were tested positive by IHT, and 33 and 17 patients were negative and borderline, respectively.

By comparing the three groups, IHT positive patients had lower age and lower SF36 vitality (V), social activities (SA), and mental summary index (MSI) than negative patients ($p<0.05$).

By comparing positive versus negative patients and by comparing positive and borderline patients versus negative patients, it was found that FACIT was higher, whereas age, SF36 V, SA, mental health (MH), and MSI were lower ($p<0.05$).

Conclusion: FMS patients present a high prevalence of neuromuscular hyperexcitability, as assessed by IHT. IHT positive patients have poor QOL and higher fatigue than IHT negative patients. Thus, IHT positivity could identify FMS patients with a more severe disease.

Keywords: Fibromyalgia syndrome, ıschemia-hyperpnea test, neuromuscular hyperexcitability, quality of life, fatigue

Introduction

Fibromyalgia syndrome (FMS) (1) is characterized by chronic widespread pain and focal tenderness sites (tender points) (2) associated with fatigue, stiffness, non-restorative sleep, irritable bowel, headache, restless legs, depression, and cognitive symptoms (3). FMS impairs quality of life (QOL) (4), sociality (5), working activities (6), and mood (7).

Because of a wide array of symptoms and the absence of specific tests confirming diagnosis, FMS is diagnosed by anamnesis and clinical examination, often years after the onset of symptoms (8). Thus, biochemical and instrumental tools that aid in diagnosis are required (9).

FMS may be included in central sensitivity syndromes (10), in which sensory perception changes in the central nervous system lead to pain exacerbation (11). In FMS, peripheral nociceptive inputs may also initiate and maintain central sensitization, thereby causing disordered central pain processing and dysfunctional pain (12, 13).

Unspecific bioptic abnormalities indicate that muscles may be involved in FMS pathogenesis (14). Muscle abnormalities may contribute to sensitization of muscle nociceptors causing pain, fatigue, and muscle weakness and may favor peripheral sensitization of afferent pain pathways, thereby providing tonic impulse input to central pathways, resulting in central sensitization (14).

Because musculoskeletal pain is a cardinal symptom of FMS, electromyography (EMG) was used to evaluate muscular physiopathology and demonstrate changes both in involved (15) and uninvolved skeletal muscles (16) in FMS with respect to controls.

EMG and, in particular, ischaemia-hyperpnea test (IHT), may detect neuromuscular hyperexcitability (NMH) (17, 18), which is defined as a reduction in the excitability threshold, that may be nonspecific or related to tetany.

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Only two studies analyzed NMH in FMS by IHT. Vitali et al. (19) demonstrated a higher prevalence of NMH, assessed after the ischemia test, in FMS than in rheumatoid arthritis. Bazzichi et al. (20) reported 25.8% of a comorbid spasmophilia in FMS patients also presenting a higher incidence of depressive and panic disorders, as assessed by DSM-IV, and a lower number of tender points than FMS patients with no spasmophilia.

The definition of spasmophilia is not univocal and its nosological identity is rather undefined. Gerson and Torunska defined spasmophilia as a latent tetany that is generally due to hypomagnesaemia or hyperventilation and not due to hypocalcemia (21, 22).

Vitali et al. (19), according to Munera et al. (23) considered NMH synonymous to normocalcemic tetany and spasmophilia and defined it as a condition characterized by motor, sensory (cramps, fasciculations, paresthaesias, rarely tetanic seizures), psychological, and visceral disturbances (19). Bazzichi et al (20) diagnosed spasmophilia based on clinical symptoms (which showed at least 1/4th of the following: cramps and/or tetanic seizures, paresthesia, tachycardia and/or dyspnea, asthenia, and dizziness) and on the positive results of IHT.

Thus, based only on IHT results, we chose to use the term NMH rather than spasmophilia.

Our principal aim is to demonstrate, the prevalence of NMH in FMS patients detected by IHT and to verify its potential utility as a diagnostic tool.

Our secondary aim is to evaluate the correlation of NMH, shown by IHT, with clinical and clinimetric parameters and to assess if FMS patients tested positive by IHT could have different characteristics with respect to patients tested negative.

Material and Methods

One hundred and forty-five FMS patients (134 women and 11 men) were recruited from the outpatient clinic of the Division of Rheumatology, Department of Experimental and Clinical Medicine, University of Florence, Azienda Ospedaliera Universitaria (AOU) Careggi.

The inclusion criterion was the diagnosis of FMS according to the American College of Rheumatology (ACR) criteria (2).

The exclusion criteria were changes in thyroid function [Free triiodothyronine (FT3), free thyroxine (FT4), Thyroid-stimulating hormone (TSH), Thyroperoxidase antibodies (ab) (TPOAb), thyroglobulin ab (TgAb), and TSHAb receptor Ab (TRAb)], electrolytes [(magnesium (Mg) and potassium (K)], and calcium (Ca) metabolism including Ca, Parathyroid hormone (PTH), and 25-hydroxyvitamin D_3 (25-OH vitamin D_3).

All patients signed an informed consent form, and procedures were conducted in accordance with the Declaration of Helsinki of 1975/83. The study was approved by our local ethics committee.

Patients were evaluated for demographic characteristic (age, sex), disease and symptoms duration, diagnosis latency, treatments, presence of headache, neurogenic hypotension, irritable bowel syndrome, irritable bladder, restless legs syndrome, thyroid function electrolytes, and calcium metabolism.

All patients were tested by standard EMG and nerve conduction studies (NCS) to rule out neuromuscular affections and with IHT to evaluate NMH (17, 24).

Patients were also assessed for pain, tenderness, disability, sleep, fatigue, QOL, anxiety, and depression by clinic and clinimetric tools.

Electromyography (EMG), nerve conduction studies (NCS), and ischaemia-hyperpnea test

EMG assesses the electrical potential formed in a muscle during its contraction [motor unit action potential (MUAP)], which reflects the activity of a group of motor units.

EMG/NCS and IHT were performed with a Synergy electromyography equipment (VIASYS HealthCare UK, Manor Way, Old Woking, Surrey, GU22 9JU, UK., 2007) by using surface electrodes for NCS and coaxial needles for EMG and IHT.

For IHT, a coaxial needle was inserted in the 1st dorsal interosseous dorsal muscle of the left hand. The examination consisted of two phases:

1. Ischaemia phase: (5 min) Caused by applying the cuff of the sphyngomanometer (blood pressure cuff) to the lower third of the arm with a pressure of 200 mgHg.
2. Hyperpnea phase: (3 min) Immediately after ischaemia, executed by inviting the patient to perform a deep hyperventilation, with a frequency of around 40 breaths/ min.

In normal subjects, no spontaneous activity is present in the muscle at rest and during IHT. A singlet is a spontaneous involuntary discharge of an individual motor unit. Spontaneous MUAPs firing in groups of two, three, or multiple potentials are defined as doublets, triplets, and multiplets. These potentials and the singlets represent the spontaneous depolarization of a motor unit or its axon.

The carpal spasm (tetany), which can be observed during the ischaemia phase, is not supported by multiplets but by EMG activity (subinterferential pattern), similar to that observed during voluntary recruitment. When doublets, triplets, and multiplets are not associated with carpal spasms or tetany, the condition is defined as non-specific NMH.

In our study, FMS patients were divided into three groups according to IHT results: positive: when doublets, triplets, or multiplets were present during hyperpnea (25); borderline: if some fasciculations and/or single doublets were present during hyperpnea; and negative: if spontaneous activity was absent (17).

Clinimetric assessment

Pain was rated with the numeric rating scale (NRS) (0-10, 0=no pain, 10=severe pain) and the regional pain scale (RPS) (score: 0-19) (26).

Tenderness was evaluated with the digital palpation of 18 tender points recognized by ACR as a criterion for FMS classification (score: 0-18) (2).

Disability was rated by the Italian versions of the Fibromyalgia Impact Questionnaire (FIQ) (score 0-100) (27, 28) and the Health Assessment Questionnaire (HAQ) (score 0-3) (29).

QOL was assessed by the Medical Outcomes Survey Short Form 36 (MOS-SF36) (30), organized into eight domains measuring physical functioning (PF), role limitations due to physical problems (PP), bodily pain (BP), general health perceptions (GH), vitality (V), social functioning (SF), role limitations due to emotional problems (EP), and mental health (MH), combined into the summary physical index (SPI) and the summary mental index (SMI); for all scales score is 0-100.

Psychological distress was assessed by the Hospital Anxiety and Depression Scale (HADS), with subscales for anxiety (HADS-a) and depression (HADS-d). For both the subscales, the scores range from 0 (no depression or anxiety) to 21 (maximal depression or anxiety) (31).

Quality of sleep was rated by NRS 0-10, with 0=the worst perceived sleep and 10=the best perceived sleep.

Fatigue was assessed by the Functional Assessment of Chronic Illness Therapy-Fatigue scale (FACIT-F) (32) (range 0-52).

Statistical analysis

Continuous and binomial variables are presented as mean±standard deviation and as numbers and percentages. The Kolmogorov-Smirnov test was used to verify the probability distribution of the samples. To compare for clinical characteristics of groups, Fischer's exact test or χ^2 test were used to test for binomial variables, and unpaired t-test and analysis of variance (ANOVA) were used to compare continuous variables in two or three groups.

The significance was set at a p-value<0.05. All analyses were performed using SPSS version 20.0 for Windows (SPSS, Chicago, IL, US).

Results

Demographic, clinical, and pharmacological characteristics of FMS patients according to results of IHT

No patient showed alterations in NCS and in EMG. According to the results of IHT, 145 FMS patients were divided in three groups: positive [95 patients (62.52%)]; negative [33 patients (22.76%)]; and borderline [17 pts (11.72%)].

Demographic and clinical characteristics and treatments are shown in Table 1.

In all FMS patients, all the parameters of thyroid function, calcium metabolism, and blood electrolytes were normal.

Age was higher in positive *versus* negative patients (p<0.05). The patients of the three groups reported a different distribution for irritable bladder disease and for the use of non-steroidal anti-inflammatory drugs (NSAIDs) and analgesics (p=0.03 in both cases).

Comparison of clinical and clinimetric characteristics of FMS patients divided in three groups (positive, negative, and borderline) according to IHT

As shown in Table 2, comparison of the three groups of FMS patients revealed the following results: age (p<0.05), SF36 V (p=0.0155), SF36 SF (p=0.0062), and SF36 MSI scores (p=0.0113) were significantly lower in positive *versus* negative patients.

No significant differences were found between positive *versus* borderline patients and between negative *versus* borderline patients.

Table 1. Demographic, clinical, and pharmacological characteristics of FMS patients according to results of IHT

	Positive (95 patients)	Negative (33 patients)	Borderline (17 patients)	p
Females	87/95 (91.59%)	31/33 (93.94%)	16/17 (94.12%)	NS
Age (years)	52.55±12.10	58.76±10.62	55.82±15.67	<0.05 (positive vs negative)
Disease duration	8.18±9.30	10.53±12.24	6.06±5.51	NS
Latency of diagnosis	6.52±7.00	6.66±10.33	5.06±5.69	NS
Irritable bowel	59/95 (62.11%)	20/33 (60.61%)	11/17 (64.71%)	NS
Irritable bladder	40/95 (42.10%)	9/33 (27.27%)	2/17 (11.76%)	0.03
Cephalalgia	69/95 (72.63%)	21/33 (63.64%)	9/17 (52.94%)	NS
Restless leg syndrome	68/95 (71.58%)	24/33 (72.73%)	12/17 (70.59%)	NS
Neurogenic hypotension	29/95 (30.53%)	7/33 (21.21%)	7/17 (41.18%)	NS
NSAIDS	47/95 (49.47%)	23/33 (69.70%)	7/17 (41.18%)	0.03
Glucocorticoids	9/95 (9.47%)	6/33 (18.18%)	1/17 (5.88%)	NS
Antidepressant	33/95 (34.74%)	12/33 (36.36%)	7/17 (41.17%)	NS
Anxiolytic benzodiazepines	24/95 (25.26%)	5/33 (15.15%)	2/17 (11.76%)	NS
Hypnotic benzodiazepines	12/95 (12.63%)	4/33 (12.12%)	3/17 (17.65%)	NS
Pregabalin	6/95 (6.32%)	1/33 (3.03%)	1/17 (5.88%)	NS
Gabapentin	5/95 (5.26%)	0/33 (0.00%)	0/17 (0.00%)	NS
Phytotherapy	12/95 (12.63%)	5/33 (15.15%)	0/17 (0.00%)	NS
Homeopathy	6/95 (6.32%)	2/33 (6.06%)	0/17 (0.00%)	NS

Continuous data are presented as mean±SD; binomial data are presented as numbers and percentages; NSAIDs: non-steroidal anti-inflammatory drugs

Comparison of clinical and clinimetric characteristics of FMS patients: positive *versus* negative according to IHT

In positive *versus* negative patients, FACIT was higher (p=0.038) and age (p=0.01), SF36 V (p=0.005), SF36 SF (p=0.002), SF36 MH (p=0.039), and SF36 MSI (p=0.004) were lower (Table 3).

Comparison of clinical and clinimetric characteristics of FMS patients: positive and borderline *versus* negative according to IHT

On comparing positive and borderline patients with negative patients, the IHT findings were similar with respect to the comparison of FMS positive *versus* negative patients.

In positive and borderline *versus* negative patients, FACIT was higher (p=0.048) and age (p=0.02), SF36 V (p=0.007), SF36 SF (p=0.002), SF36 MH (p=0.036), and SF36 SMI (p=0.003) were lower (Table 4).

Discussion

In our study, the results of IHT were positive in >60% of FMS subjects, indicating the presence of NMH in the majority of patients.

Because all subjects demonstrated normal calcium metabolism, independent from test results (positive, borderline, or negative), NMH was not linked to hypocalcemia and/or hypoparathyroidism. Moreover, demographical and clinical characteristics were homogeneous among groups because only age was higher in positive versus negative patients.

Our results are different from those shown by Bazzichi et al. (20); we diagnosed spasmophilia in 25.80% of FMS patients. This difference is observed because we have assessed NMH only by IHT, whereas Bazzichi et al (20). diagnosed spasmophilia as a comorbid and distinct condition of FMS, based on both clinical and EMG criteria. Vitali et al (19) found at least two clinical features of spasmophilia in 39% of FMS patients and a

Table 2. Clinical and clinimetric characteristics of FMS patients divided in three groups (positive, negative, and borderline) according to IHT

	Positive	Negative	Borderline	ANOVA overall effect	p vs. n	p vs. B	n vs. B
HADS-A	10.80±4.47	9.70±3.90	10.19±4.18	NS	NS	NS	NS
HADS-D	9.10± 4.86	8.58±4.58	9.25±3.59	NS	NS	NS	NS
HADS-TOT	19.88±8.74	18.27±7.74	19.44±7.15	NS	NS	NS	NS
Sleep quality	4.35±2.42	4.62±2.26	4.82±2.43	NS	NS	NS	NS
Pain	5.86±2.53	5.67±2.55	6.24±3.08	NS	NS	NS	NS
Tender points	15.63±3.85	14.74±4.18	15.72±3.41	NS	NS	NS	NS
FIQ	54.49±19.03	49.01±20.72	54.45±22.56	NS	NS	NS	NS
HAQ	1.13±1.41	0.85±0.57	2.15±5.41	NS	NS	NS	NS
FACIT	24.61±10.83	20.06±9.64	22.29±10.01	NS	NS	NS	NS
SF36 PF	49.83±22.87	54.85±23.93	52.50±25.82	NS	NS	NS	NS
SF 36 PP	21.51±31.66	34.85±40.96	31.25±38.19	NS	NS	NS	NS
SF36 BP	30.83±16.59	37.45±20.76	33.35±24.98	NS	NS	NS	NS
SF36 GH	35.77±21.84	37.15±20.24	35.31±18.35	NS	NS	NS	NS
SF36 vitality	30.29±20.41	42.33±21.60	36.25±16.68	0.0155	<0.05	NS	NS
SF36 SF	44.34±23.16	60.36±28.27	49.81±18.69	0.0062	<0.05	NS	NS
SF 36 EP	33.10±38.13	45.88±40.93	26.88±32.52	NS	NS	NS	NS
SF36 MH	46.4±20.86	55.18±19.85	48.75±13.24	NS	NS	NS	NS
SF36 SPI	32.22±8.37	34.03±10.15	33.81±11.34	NS	NS	NS	NS
SF36 SMI	34.01±11.27	40.94±11.62	35.00±7.83	0.0113	<0.05	NS	NS
RPS	13.58±4.30	12.03±5.22	13.29±5.59	NS	NS	NS	NS
Tender points	15.63±3.85	14.74±4.18	15.57±4.02	NS	NS	NS	NS

Continuous data are presented as mean±SD; HADS: hospital anxiety and depression scale; HADS-a: HADS subscale for anxiety; HADS-d: HADS subscale for depression; FIQ: fibromyalgia impact questionnaire; HAQ: health assessment questionnaire; FACIT: functional assessment of chronic illness scale; SF36: short form 36; SF36 PF: physical functioning; SF36 PP: role limitations due to physical problems; SF36 BP: bodily pain; SF36 GH: general health perceptions; SF36 V: vitality (V); SF36 SF: social functioning; SF36 EP: role limitations due to emotional problems; SF36 MH; mental health (MH); SF36 SPI: summary physical index; SF36 SMI: summary mental index; RPS: regional pain scale

post-ischemic spontaneous EMG hyperactivity in 22.45% of FMS patients (19). In our opinion, symptoms such as paresthesia, muscle stiffness and contractures, cramps, tachycardia, dyspnea, asthenia, and dizziness, other than anxious and panic crisis and restless legs syndrome, could be part of the wide array of FMS manifestations (2) rather than being representative of spasmophilia.

It should also be noted that IHT is not standardized; therefore, the procedures and the devices may be different according to the studies, and the results may not be easily comparable.

Bazzichi et al. (20) used surface electromyography (SEMG) and defined IHT positivity in the presence of doublets, triplets, and multiplets after the application of 10 min of ischaemic stimulus (pressure >20 mmHg of the patient's systolic blood pressure, by a blood pressure cuff of a sphyngomanometer) or during 3 min of hyperpnea.

Vitali et al. (19) also used SEMG and applied only ischaemia stimulus (pressure of 20-30 mmHg above systolic blood pressure) and defined IHT positivity in the presence of multiplets during a 3.30-4 min post-ischemic period of monitoring.

Conversely, we used coaxial needles, and IHT was considered positive at the onset of spontaneous motor activity (indicated as doublets, triplets, and multiplets) during the ischaemia and hyperpnea phase. In our case, ischaemia was induced by applying a pressure of 200 mgHg by the cuff of the sphyngomanometer for 5 min (17, 24).

We know that hyperventilation determines respiratory alkalosis with an increase in arterial pH, leading to a decrease in the free ionized Ca level in the plasma (18, 20) and that hypocalcaemia alone can induce paraesthesiae and may determine spontaneous activity such as fasciculation and/or poliplets by modifying membrane excitability.

We can hypothesize that the onset of fasciculation or/and poliplets in FMS patients relies on the different excitability of muscle membrane (33) and/or axon membrane (18) shown in FMS with respect to controls, which leads to NMH.

In agreement with the literature, all our FMS patients demonstrated impaired QOL, disability, and fatigue (4-6, 34). Clinimetric results were differently impaired by stratifying patients according to the results of IHT. By comparing positive with negative and borderline patients, patients tested positive by IHT had poor scores in vitality, social functioning, and in overall mental QOL than patients tested negative by IHT.

By comparing only positive *versus* negative patients, these results were confirmed and also differences in fatigue and mental health (worse in positive than in negative patients) were shown.

NMH, as defined by positivity at IHT, is present in majority of our FMS patients and identifies patients in which fibromyalgic symptoms cause a higher distress, leading to QOL impairment.

Table 3. Clinical and clinimetric characteristics of FMS patients: positive versus negative according to IHT

	Positive	Negative	p
Age	52.55±12.10	58.76±10.62	0.0101
Disease duration	8.18±9.30	10.53±12.24	NS
Latency	6.52±7.0	6.66±10.33	NS
HADS-A	10.80±4.47	9.70±3.90	NS
HADS-D	9.10±4.86	8.58±4.58	NS
HADS-TOT	19.88± 8.74	18.27±7.74	NS
Sleep quality	4.35±2.42	4.62±2.26	NS
Pain	5.86±2.53	5.67±2.55	NS
FIQ	54.49±19.03	49.01±20.72	NS
HAQ	1.13±1.41	0.85±0.57	NS
FACIT	24.61±10.83	20.06±9.64	0.0377
SF36 PF	49.83±22.87	54.85±23.93	NS
SF 36 PP	21.51±31.66	34.85±40.96	NS
SF36 BP	30.83±16.59	37.45±20.76	NS
SF36 GH	35.77±21.84	37.15±20.24	NS
SF36 V	30.29±20.41	42.33±21.60	0.0054
SF36 SF	44.34±23.16	60.36±28.27	0.002
SF 36 EP	33.10±38.13	45.88±40.93	NS
SF36 MH	46.40±20.86	55.18±19.85	0.039
SF36 SPI	32,22±8.37	34.03±10.15	NS
SF36 SMI	34.01±11.27	40.94±11.62	0.004
RPS	13.58±4.30	12.03±5.22	NS
Tender points	15.63±3.85	14.74±4.18	NS

Continuous data are presented as mean ± DS; HADS: hospital anxiety and depression scale; HADS-a: HADS subscale for anxiety; HADS-d: HADS subscale for depression; FIQ: fibromyalgia impact questionnaire; HAQ: health assessment questionnaire; FACIT: functional assessment of chronic illness scale; SF36: short form 36; SF36 PF: physical functioning; SF36 PP: role limitations due to physical problems; SF36 BP: bodily pain; SF36 GH: general health perceptions; SF36 V: vitality (V); SF36 SF: social functioning; SF36 EP: role limitations due to emotional problems; SF36 MH; mental health (MH); SF36 SPI: summary physical index; SF36 SMI: summary mental index; RPS: regional pain scale

Fatigue, both due to and causing disability, is one of the cardinal features of FMS. It is related both to tiredness (of central origin) and to peripheral muscle fatigue (34). Our FMS patients with NMH presented major fatigue at FACIT and lower vitality scores at SF 36 (meaning high fatigue) than patients tested negative by IHT.

Concordantly with previous data (20), no differences in FMS groups according to IHT results were found in disability.

Bazzichi et al. (20) found patients with spasmophilia and FMS as having higher tender point counts than subjects with FMS alone. In our study, referred pain and tenderness were not different according to test results. This confirms that IHT positivity is more related to general distress than to peripheral pain and tenderness.

We showed that anxious and depressive symptoms, evaluated by HADS, were not different according to the test results. This is concordant with Bazzichi et al. (20), who found a similar percent of anxiety and depression as self-reported symptoms in both groups. However, in this study, when FMS patients were administered with the structured clinical interview for Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV), those tested negative by IHT were significantly more affected by psychiatric comorbidities (indicated by depression and panic disorders) than positive patients (20). The authors explain this discrepancy as due to a distortion of mood perception present in both groups of patients.

The diagnosis of FMS is still difficult, under-estimated, and often delayed (8); therefore, tests that are able to confirm or facilitate the diagnosis are required (9).

Based on bioptic, metabolic, and molecular studies, muscles are retained as involved in FMS diagnosis (14). Sensitization of muscle nociceptors may cause pain, fatigue, and muscle weakness and results in peripheral sensitization of afferent pain pathways, thereby providing tonic impulse input to central pathways and leading ultimately to central sensitization (14).

EMG, used in different studies to evaluate muscular physiopathology in FMS, revealed altered muscle fiber conduction velocity (CV) in involved muscles (15) and high muscle membrane CV in muscles not involved in FMS (33), suggesting an overall muscular membrane disorder and electrical manifestation of muscle fatigue (16, 34).

IHT may detect NMH, defined as a reduction in the threshold of excitability of skeletal muscles (17, 18). From our results, we may hypothesize that NMH is common in patients with FMS and IHT could be helpful in diagnosing FMS.

We may also infer IHT positivity helps to identify FMS patients with lower QOL, higher fatigue, higher distress, and disease severity. IHT positivity may also be useful in better tailoring treatment interventions, particularly non pharmacological treatments such as mind body therapies, dealing efficaciously with disability, psychological distress, fatigue, and exercises (35).

Limitations of our study can be the absence of a control group; however, this group is neither present in previous studies assessing IHT in FMS (19, 20) nor in its transversal design. Future studies on wider cohorts of patients and with longitudinal design are required to confirm the efficacy of IHT in FMS, its eventual change over time, and its relationship with psychological, physical, and disease-associated problems.

In conclusion, >60% of our FMS patients have IHT positivity, indicating a high prevalence of NMH.

Patients positive to the test have poor QOL and higher fatigue than those negative to the test. Thus, we may also infer that IHT positivity could help diagnose FMS and identify patients with a

Table 4. Clinical and clinimetric characteristics of FMS patients: positive and borderline versus negative according to IHT

	Positive+Borderline	Negative	p
Age (years)	53.05±12.69	58.76±10.62	0.02
Disease duration	7.86±8.84	10.53±12.24	NS
Latency	6.30±8.31	6.66±10.33	NS
HADS-A	10.78±4.42	9.70±3.90	NS
HADS-D	9.12±4.68	8.58±4.58	NS
HADS-TOT	19.82±8.50	18.27±7.74	NS
Sleep quality	4.43±2.42	4.62±2.26	NS
Pain	5.92±2.61	5.67±2.55	NS
FIQ	54.48 ±19.50	49.01±20.72	NS
HAQ	1.28±2.46	0.85±0.57	NS
FACIT	24.25±10.70	20.06±9.64	0.048
SF36 PF	50.25±23.24	54.85±23.93	NS
SF 36 PP	23.04±32.75	34.85±40.96	NS
SF36 BP	31.21±18.03	37.45±20.76	NS
SF36 GH	35.70±21.24	37.15±20.24	NS
SF36 V	31.23±19.92	42.33±21.60	0.007
SF36 SF SF	45.20±22.53	60,36±28,27	0.002
SF 36 EP	32.13±37.23	45.88±40.93	NS
SF36 MH	46.76±19.83	55.18±19.85	0.036
SF36 SPI	32.48±8.86	34.03±10.15	NS
SF36 SMI	34.17±10.77	40.94±11.62	0.003
RPS	13.53±4.50	12.03±5.22	NS
Tender points	15.60±3.63	14.74±4.18	NS

Continuous data are presented as mean±SD; HADS: hospital anxiety and depression Scale; HADS-a: HADS subscale for anxiety; HADS-d: HADS subscale for depression; FIQ: fibromyalgia impact questionnaire; HAQ: health assessment questionnaire; FACIT: functional assessment of chronic illness scale; SF36: short form 36; SF36 PF: physical functioning; SF36 PP: role limitations due to physical problems; SF36 BP: bodily pain; SF36 GH: general health perceptions; SF36 V: vitality (V); SF36 SF: social functioning; SF36 EP: role limitations due to emotional problems; SF36 MH; mental health (MH); SF36 SPI: summary physical index; SF36 SMI: summary mental index; RPS: regional pain scale

more severe disease and may also be useful in better tailoring treatments.

Ethics Committee Approval: Ethic committee approval was received for this study from our Local Ethical Committee.

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - S.M.B., A.D.R.; Design - S.M.B., A.D.R.; Supervision - G.D.S.; Materials - D.L., M.O.; Data Collection and/or Processing - A.D.R., D.L., M.O.; Analysis and/or Interpretation - S.M.B., A.D.R, D.L., M.O., G.D.S.; Literature Review - D.L., M.O.; Writers - A.D.R., D.L.; Critical Review - G.D.S., S.M.B.

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