Outcome of small fibre pathology in fibromyalgia: a real life longitudinal observational study

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Abstract

Objective

Small fibre pathology is frequently described in fibromyalgia (FM), but its evolution and its role in clinical outcome of the disease are unclear. This longitudinal observational real-life study aimed to monitor the evolution of skin nerve fibre density in FM, in view of the clinical data.

Methods

Sixty-two FM patients were controlled by means of skin biopsy and clinical assessment after 18 months of follow-up.

Results

At T0 intraepidermal nerve fibre density (IENFD) was normal in 10 patients, reduced at thigh-proximal-site in 46 cases and decreased at proximal and foot-distal-site in 6 patients. At follow up-T1-the IENFD was unchanged, while Brief Pain Inventory-BPI-pain sub score, DN4 and fatigue were improved. Reduced IENFD at proximal and distal sites, together with fatigue and BPI-motor and work sub scores were predictors of more severe disability measured with Fibromyalgia Impact Questionnaire (FIQ) at T1. Reduced IENFD influenced a minor effect of drugs-antiepileptics and/or antidepressants, and physical exercise on fatigue.

Conclusion

Small fibre impairment seems stable in medium term in FM. A possible influence of small fibre dysfunction on motor performance could have a role in FM evolution. The beneficial effect of physical exercise could be limited in patients with reduced IENFD.

Key words

fibromyalgia, skin biopsy, clinical evolution

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Introduction

Fibromyalgia (FM) is a condition of chronic and widespread pain, accompanied by fatigue, sleep disorders, loss of concentration, mood changes and various symptoms and signs of vegetative dysfunction. Unfortunately, to date, the diagnostic criteria are purely clinical (1). Dealing with FM is currently a challenge, in the absence of a useful marker to objectify in a simple and routine way the presence of the pathology, to allow the development of targeted therapies and to ensure the social recognition of a chronic and disabling condition.

Neurophysiological methods and skin biopsy, mostly used for research purposes, have shown alterations of the central and peripheral systems in FM. In fact, FM is part of the group of central sensitisation syndromes, characterised by alteration in the central processing of pain (2). More recently, abnormalities of small nerve fibres have raised new questions about the pathogenesis of FM, the diagnostic role of skin biopsy and the therapeutic possibilities (3, 4). Methods useful to examine sensory nerves, as ultrasonographic data of sural nerve, confirmed that FM could have a neuropathic origin (5). Recent studies suggested that small fibre pathology does not affect the clinical phenotype in FM patients (6, 7). However, Evdokimov *et al*. (8) showed more severe clinical impairment in FM patients with neuropathic suffering. Longitudinal studies in FM cohorts showed a substantial stability or mild improvement of global clinical impairment over time (9, 10, 11). Studies on the evolution of small fibre pathology and the possible influence on clinical outcome are currently lacking.

This is the first observational real-life study aiming to evaluate the evolution of skin nerve fibre density in FM, in view of clinical data.

We thus followed for 18 months a cohort of FM patients, whose data from first visit were described in Vecchio *et al*. (6).

Methods

Subjects

Patients were selected for the basal evaluation (here defined as T0) between January and December 2017. Data are reported in Vecchio *et al*. (6). The clinical and skin biopsy follow-up were performed after 18 months of clinical observation, between December 2018 and April 2021. All the enrolled subjects signed informed consent, and local Ethical Committee approved the observational study on clinical assessment and skin biopsy follow up, that is included in the routine clinical activity. During the one year and a half observation, patients underwent an in-person visit at 6 and 12 months, to re-evaluate the clinical conditions, compliance and effects of treatment. We also contacted patients by phone or e-mail at months 3 and 9 (Fig. 1).

As reported in our previous study, inclusion criteria consisted in a diagnosis of FM, according to ACR Diagnostic Criteria for Fibromyalgia published in 2010 (12). Exclusion criteria were the following: low level of education (below 8 years), drugs acting on the central nervous system at baseline, a prior history of any other neurological conditions, active and inactive cancer, diabetes, renal impairment, active autoimmune/inflammatory/rheumatological disease, psychiatric disorders except for mild anxiety and depression. We excluded patients with a Self-Rating Depression Scale (SDS) ≥50 and an Anxiety Scale (SAS) ≥45.

Clinical tests

We tested patients with the following scales: Visual Analogue Scale (VAS) (13), Zung SDS and SAS (14, 15), Fibromyalgia-linked invalidity questionnaire (FIQ) (16), Neuropathic Pain Diagnostic Questionnaire (DN4) (17), Multidimensional Assessment of Fatigue (MAF) (18), and the Brief Pain Inventory (BPI) with pain severity and interference subscores (19). Diagnosis of FM was done in agreement with 2010 criteria, using the Wide Pain Index (WPI) and Symptoms Severity Scale (SS) (12).

Therapeutic management: three expert neurologists managed patients during the follow-up. In accordance with the routine approach of our Centre, all patients were suggested to take pharmacological treatment with antiepileptics

Fig. 1. Flow chart reporting clinical assessment of patients during the follow-up.

(pregabalin 150–300 mg) and antidepressants (duloxetine 60 mg) (20).

We also prescribed tramadol 100–200 mg or tapentadol 100–200 mg/die for 15–20 days during pain exacerbation. All patients were recommended to follow a programme of aerobic exercise, consisting of 45' min brisk walking and/or cycling and/or swimming four times weekly. The physical activity should be intense enough to provoke slight sweating. We ascertained the compliance to physical programmes, during the visits and phone contacts at month 9 and 15.

Skin biopsy

As reported in previous studies (6) patients underwent 3-mm punch biopsies from the thigh and distal leg following an intradermal injection of 1% xylocaine. Briefly, the specimens were fixed in 2% paraformaldehyde-lysine-sodium periodate, at 4°C overnight, following which they were cryoprotected, serially cut with a cryostat, and immunostained using polyclonal anti-protein gene product 9.5 (Ultraclone Ltd). We calculated the intraepidermal nerve fibre density on three non-consecutive central sections by bright-field microscopy, using a stereology workstation (Olympus BX50, PlanApo oil-objective 40x/NA = 1.0), and compared them to sex-and age-adjusted normative values (22-24). On the basis of the cut-off values (22-24), patients were classified into those with proximal reduced IENFD-P-, distal and proximal reduced IENFD-D- and normal IENFD-N-). The same criteria was used at follow up to define patients as stable, improved or worsened based on the above reported classification and cut-off values (23, 24). In any case, the appearance of degenerative aspects determined a judgment of worsening.

Table I. Main clinical and demographic features in FM patients evaluated at follow-up.

	Mean	SD
WPI	13.13	4.64
SS	7.39	2.59
Age (years)	51.14	9.23
Disease duration (years)	9.69	7.21
4 males. 58 females		

WPI: wide pain index; SS: symptoms severity.

Statistical analysis

We used the Student's t-test for paired data to evaluate the evolution of IENFD and main clinical features (FIQ, BPI Fatigue, NRS, DN4, anxiety and depression).

To understand if the small fibre denervation at T0 could influence the clinical evolution after 18 months, we used the repeated measures ANOVA (complete factorial model, sum of squares type III) with the groups with normal skin biopsy, proximal denervation and proximal plus distal denervation (N, P or D) at T0 as factor and main clinical features (T0 *vs*. T1) as variables.

The same analysis was performed using stable, improved or got worse IENFD groups as factor.

To understand which variable would have predicted the outcome of fibromyalgia disability measured with the FIQ at T1, we used a multiple regression model introducing proximal and distal IENFD, WPI, SS, fatigue, BPI, SAS, SDS, NRS, age and illness duration at T0. The effect of treatments was evaluated with a MANCOVA model (complete factoria, type III sum of squares), using main clinical features (fatigue, BPI, DN4, SAS, SDS and NRS) as variables, and the phase T0 *vs*. T1, the pharmacological treatments AED *vs*. AD *vs*. AED+AD and the aerobic exercise yes *vs*. not as factors. We introduced the values of proximal and distal IENFD at T0 as covariates.

Results

Patients

Among the 81 patients clinically evaluated and with skin biopsy (6), 62 of them regularly completed the observation period. Five patients did not give the consent for the control biopsy, and 15 were lost at the follow-up (Table I, Fig. 1). Among them, 1 had changed residence, 3 did not observe regularly the appointments because of the pandemic restrictions, the remainder, reporting side effects or treatment inefficacy at the previous clinical control, did not observe the scheduled appointment, or even decided to change medical team or hospital. The mean interval for the follow-up was 72±3.2 weeks.

Table II. Number of cases with normal skin biopsy (N), proximal denervation (P) and proximal and distal denervation (D) at T0 and T1.

		Skin biopsy T1			Total
		N	P	D	
Skin biopsy T0	N	6	3	1	10
	P	4	39	3	46
	D	1	3	2	6
Total		11	45	6	62

Most of the patients were in the P group at T0 and remained stable at T1 (chi square 19.99 DF 4 $p<0.001$).

Table III. IENFD at thigh-proximal site (P) and Foot-distal site (D) in 62 FM patients in basal condition and after 18 months follow-up. Results of Student's t test for paired data were not significant.

	Mean	SD	t	*p*
P density T0	9.77	3.07	-1.47	0.14
P density T1	10.29	3.02		
D density T0	8.11	2.72	0.49	0.62
D density T1	7.93	2.69		

Skin biopsy

At T0, most of the patients presented with small fibre denervation at proximal site. At T1, patients with an IEFND above the cut-off at both proximal and distal sites prevailed, though three of them got worse and presented also with denervation at distal site. Among 6 patients with denervation at proximal and distal sites at T0, 1 showed an IEFND above the cut-off and 3 evolved into denervation limited to the proximal site at T1. Four patients with normal skin biopsy at T0, presented with denervation at T1, 3 cases at proximal site and 1 case at proximal and distal sites. (Table II). Considering the FM patients as a whole, the IENFD remained stable at the follow-up (Table III, Fig. 2).

Clinical evolution

- Main clinical features

At follow-up, WPI and SS remained stable. Patients improved in BPI-pain, DN4 and fatigue. Anxiety and depression, as measured with SAS and SDS, showed a tendency through worsening, significant for anxiety (Table IV). The FIQ and NRS scores remained stable. The other BPI indexes did not change at follow-up. (Table IV)

- Relationship between IENFD and clinical evolution

In order to understand if the improvement of BPI-Pain was different in FM patients grouped for skin biopsy at T0, we used the ANOVA for repeated measures comparing the BPI-Pain between T0 and T1 among the groups N *vs*. P *vs*. D. We found that there was no significant effect of follow-up, while intergroups differences emerged. In fact, patients in the N group had lower BPI-Pain scores either in basal or at follow-up, with a significant difference in comparison with D group. (Results of repeated ANOVA: T0 *vs*. T1 x skin biopsy groups at T0 F 0.31, *p*=0.72; inter-subjects effect: F 3.46, *p*=0.039. Bonferroni test: N *vs*. D 0.036; P *vs*. N and *vs*. D: ns-Fig. 3). The evolution of IENFD did not influence the outcome of the BPI-Pain scores, as stated by repeated measures ANOVA using stable, improved or got worse IENFD groups as factor.

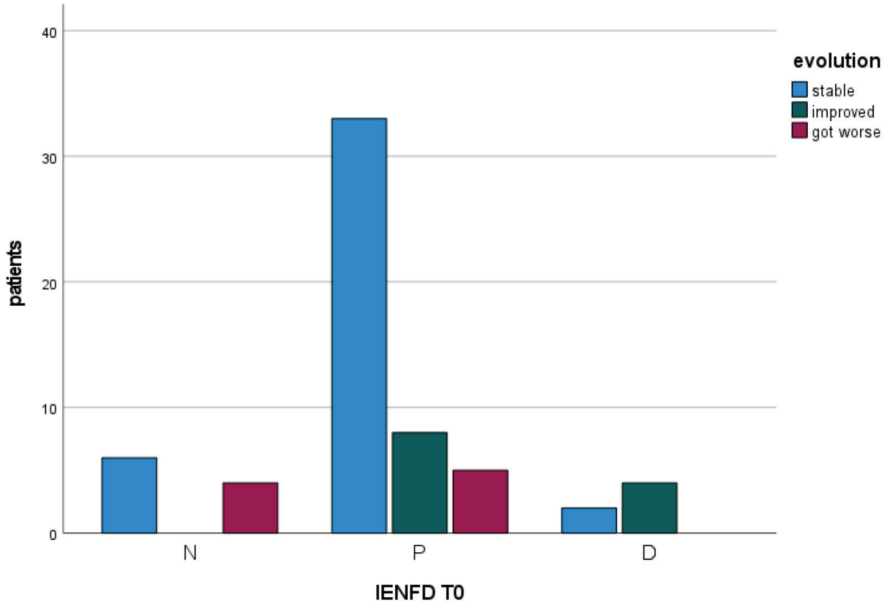

Fig. 2. Evolution of IENFD in 62 FM patients after 18 months follow-up. Most of the patients remained stable. N: patients with normal skin biopsy at T0, P patients with denervation at proximal site at T0, D patients with denervation at proximal and distal sites at T0.

Table IV. Evolution of main clinical variables after 18 months follow-up. Results of Student's t-test for paired data are reported. Significant results are in bold.

		Mean	SD	t	*p*
BPI-pain	T0	34.26	8	2.96	0.002
	T1	30.60	5.39		
BPI- motor	T0	20.77	5.45	0.82	0.41
	T1	19.66	5.71		
BPI-work	T0	20.79	5.38	1.44	0.078
	T1	19.74	4.86		
Fatigue	T0	37.69	8.14	1.93	0.029
	T1	33.85	12.48		
FIQ	T0	59.34	14.33	-0.18	0.49
	T1	59.38	13.06		
NRS	T0	7.00	1.59	0.67	0.25
	T1	6.81	1.82		
SAS	T0	43.96	7.53	-2.36	0.011
	T1	46.94	5.7		
SDS	T0	44.9	6.7	-1.47	0.14
	T1	46.7	5.7		
DN4	T0	4.82	2.19	3.66	<0.001
	T1	3.68	1.49		

Fatigue improved at follow-up, but this was independent from the presence of small fibre neuropathy at T0. Patients in the D group showed higher fatigue scores either at T0, or at T1, but this did not reach the statistical relevance. Results of repeated ANOVA: T0 *vs*. T1 x skin biopsy group N *vs*. P *vs*. D F 0.35, *p*=0.72; intra-subjects effect: F 2.29, *p*=0.059. Bonferroni test: n.s.

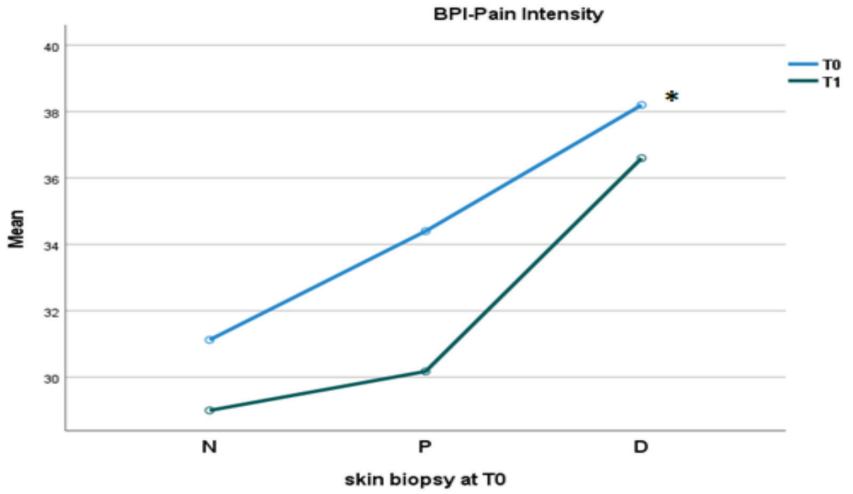

Fig. 3. BPI-pain intensity scores at T0 and T1 in the 3 IENFD (N normal, P denervation at proximal site, D denervation at distal site) groups as identified at T0.
Results of Bonferroni test: *D *vs*. N and $p<0.05$.

Table V. Multi-regression analysis with FIQ (Fibromyalgia Impact Questionnaire) at T1 as predictable variable and main clinical characteristics at T0 as predictive factors.

	B	Standard error	Beta	t	Sign.
(Costant)	53.948	22.546		2.393	.023
Duration	0.011	0.288	0.007	0.038	0.970
P Density	2.192	1.004	-0.494	-2.184	0.037
D Density	-3.784	1.047	-0.881	-3.614	0.001
SAS	0.096	0.292	0.060	0.327	0.745
SDS	0.351	0.378	0.190	0.929	0.360
Fatigue	0.049	0.227	0.344	2.181	0.037
DN4	2.213	0.870	0.406	2.544	0.016
BPI pain	0.589	0.289	0.378	2.042	0.050
BPI motor	1.159	0.477	0.523	2.432	0.021
BPI work	1.703	0.535	0.698	3.184	0.003
WPI	0.489	0.456	0.177	1.071	0.292
SS	1.293	0.632	0.299	2.048	0.049
NRS	0.49	0.45	0.116	1.061	0.28

P: proximal; D: distal; SAS: Zung Anxiety Scale; SDS: Zung Depression Scale; BPI: brief pain inventory; WPI: wide pain index; SS: symptoms severity; NRS: numerical rating scale.

The DN4 score improved independently from the IENFD group (results of repeated ANOVA: T0 *vs*. T1 x skin biopsy group N *vs*. P *vs*. D F 3.06 p=0.86; intra-subjects effect: F 0.65, p=0.52). The evolution of IENFD did not influence the DN4 improvement at follow-up.

-Variables influencing the evolution of FM invalidity: results of multiple regression analysis. The multi-regression analysis, which included FIQ at T1 as the predictable variable, and age, duration, WPI, SS, IENFD at proximal and distal sites, SAS, SDS, BPI, NRS, DN4 and fatigue at T0 as predictors, was significant (r=0.69 r square 0.28 ANOVA F 2.45, p=0.022). Taking into consideration single predictors, the proximal and distal IENFD, fatigue, DN4 score, BPI motor and work sub scores and SS (associate symptoms) at T0 corresponded to more severe disability at T1 (Table V, Fig. 4).

Effects of treatments
At T0, clinicians prescribed duloxetine 60 mg in 7 patients and pregabalin 150 mg in 55 patients (20). Short-term use of tramadol/tapentadol (100-200 mg for 7–10 gg) was recommended during exacerbation of pain. Clinical profile was quite similar among patients treated with AD and AED, except for slightly higher levels of anxiety and depression in AD-treated patients. We suggested aerobic exercise to all patients. At 6th month and 12th month clinicians prescribed the association between pregabalin 150/300 mg and duloxetine 60 mg, on the basis of patients' subjective impression of no improvement. At T1 patients under combined treatment were 24, 33 used pregabalin 150/300 mg, 5 duloxetine 60 mg. At T1, 20 patients had assumed episodically tramadol or tapentadol. At T1, only 22 patients confirmed a regular aerobic exercise. Among patients observing regular physical exercise, 9 were in the N group, 12 in the P group and 1 patient in the D group (Fig. 5).
A Mancova analysis evaluated the effects of main pharmacological treatments (AED+AD, AD, AED), aerobic exercise (AF yes, not) and phase (T0, T1) on main clinical variables (DN4, BPI,-motor, work, pain, FIQ, fatigue), using IENFD as covariate. We found a significant global effect for phase, IENFD and treatments (Table VI). In particular, reduced IENFD corresponded to increased BPI-work score (Supplementary Table S1). The covariates IENFD influenced the clinical profile of patients under different treatments and the clinical outcome of patients observing or not a programme of physical exercise. In particular, at follow-up, fatigue improved in patients with higher IENFD, for effect of physical exercise (Suppl. Table S1 and 2, Fig. 6).
Patients with combined AED + AD therapy seemed to have less effect on fatigue at follow-up, particularly those with more compromised skin biopsy (Fig. 7).

Discussion

At the best of our knowledge, this is the first study evaluating the evolution of small fibre sufferance and its possible impact on clinical symptoms and therapeutic response in a cohort of FM patients.
Skin biopsy remained substantially stable over time, as well as clinical features, with a mild improvement of fatigue, pain related disability and DN4 score. Reduced epidermal fibre density at proximal and distal sites, together with clinical variables as fatigue and work limitation, are associated with more severe disability at follow up. A

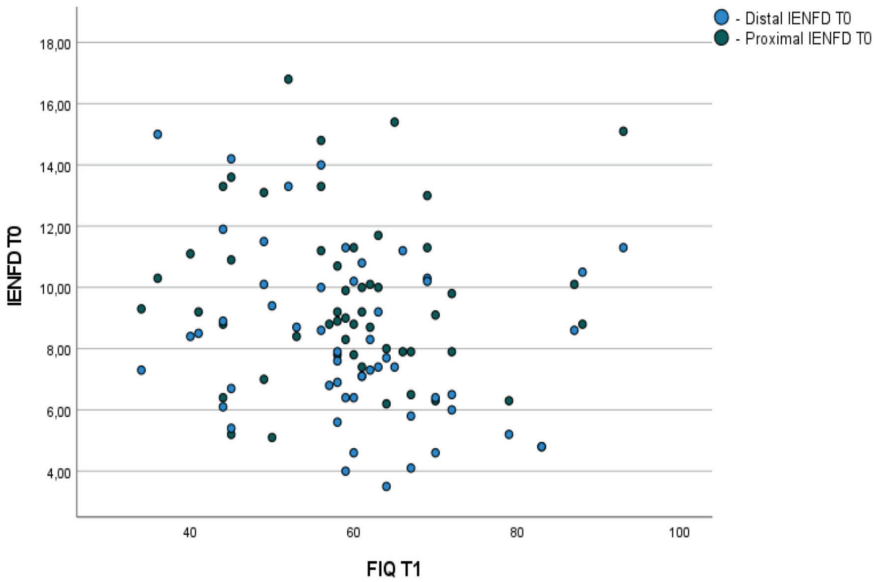

Fig. 4. Linear dispersion between IENFD at thigh (proximal) and foot (distal) sites at T0 and Fibromyalgia Impact Questionnaire (FIQ) at T1.

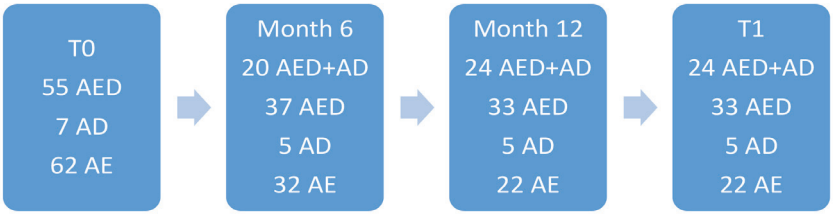

Fig. 5. Therapies employed at T0, month 6, month 12 and T1.
AED: antiepileptic drugs (pregabalin); AD: antidepressants (duloxetine); AF: aerobic exercise.

normal IENFD conditioned a better response to aerobic exercise.

Evolution of skin biopsy and clinical symptoms

The IENFD did not change or get worse after 18 months follow-up in the majority of FM patients. The relevance of small fibre impairment in FM patients is still matter of debate (25). Clinical picture is dissimilar from small fibre neuropathy (SFN), which present with pain of neuropathic type, prevalent at distal sites (7). In previous studies, idiopathic SFN showed a progressive decrease of IENFD at proximal and distal sites after on average 2 years follow-up, similar to patients with SFN secondary to impaired glucose tolerance and diabetes mellitus (26). The stability of IENFD over time confirms that FM may not be defined as a subtype of SFN, at least in the majority of patients. In our series, the few patients with proximal and distal reduced intraepidermal fibre density, remained stable or even improved after 18 months follow-up, which suggested that also this small subgroup did not show an evolution similar to SFN.

The clinical picture was stable in our FM patients, in accord with previous longitudinal studies in large cohorts. Those studies demonstrated that, in any case, stress and physical inability influenced a poorer clinical evolution (9-11). Long-term longitudinal evaluation of idiopathic SFN, showed that most patients do not develop major neurologic impairments and disability but a higher mortality risk from disease onsets, probably for vegetative impairment (27). Studies on mortality risk in FM, showed causes not directly associated to worsening of somatic or vegetative symptoms, rather to accident or suicidal, linked to psychiatric comorbidities and stressful events (28).

Despite fatigue, invalidity linked to pain and neuropathic aspects as measured with DN4 got better in our patients, the FIQ score did not improve but remained stable. A complex interaction of multiple factors, may influence the global outcome of the disease (28). In our FM patients, anxiety scores got worse at follow-up, though patients assumed AED and/or AD. However, anxiety and depression alone did not predict the disability at follow-up. Limitation in work and motor capacities and fatigue were associated to more severe disability at follow-up. Small fibre impairment seems also to have a role in the evolution of FM, being associated to more severe disability. In our previous study, a correlation between limitation in motor performances and small fibre sufferance emerged (6). In the present study, we can confirm that patients who presented with motor difficulty, fatigue and small fibre involvement, had higher global disability at follow-up. In movement disorders, a correlation exists between motor capacity and small fibre pathology (29). The longitudinal follow-up of Parkinson's disease patients, demonstrated that motor rehabilitation improved peripheral nerves pathology (4).

Apart from the well-known interaction between pain sensation and movement limitation which characterises FM patients (30-32), small fibre pathology could also directly induce motor impairment and global disability for an altered control of posture and gait (29). Another element in favour of the hypothesis that small fibre impairment could influence motor performance is the observation that patients with normal IENFD had also a more evident clinical advantage from physical exercise, probably for less limitation in the execution of the aerobic programme we prescribed.

Effects of treatments. This was an observational study reporting data from clinical routine activity. Clinicians followed the current therapeutic recommendation for drugs prescription (20). The general efficacy of treatments in FM is outside the aim of the present study, focusing on possible different clinical evolution in patients with small fibre pathology. Based on these data, we cannot establish if the mild improvement of fatigue, DN4 and in-

Table VI. Results of MANCOVA analysis with DN4, BPI, motor, work, pain, FIQ, fatigue as variables and IENFD as covariate. Details of intra subject effect are reported in Table I.

	Roy square	Value	F	DF	Error DF	Sig.
Main effect		3.064	44.936	6	88	<0.001
IENFD proximal		0.175	2.567	6	88	0.024
IENFD distal		0.228	3.349	6	88	0.005
Phase T0 *vs*. T1		0.326	4.787	6	88	<0.001
Physical exercise						
Yes *vs*. Not		0.056	0.818	6	88	0.559
Therapy						
AED *vs*. AD *vs*. AED+AD		0.338	5.021	6	89	<0.001
Phase T0 *vs*. T1 *physical exercise yes *vs*. not	0.166	2.438	6	88	0.032	
Phase T0 *vs*. T1 *	0.197	1.620	12	178	0.089	

Therapy AED *vs*. AD *vs*. AED+AD.

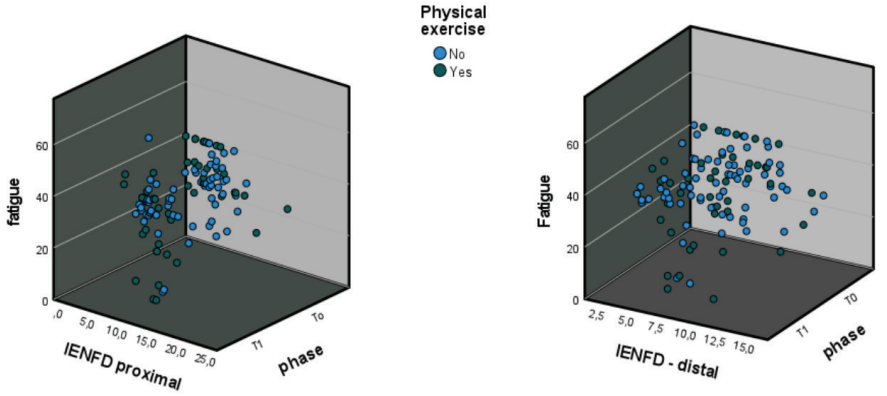

Fig. 6. Outcome of fatigue in relation to intraepidermal nerve fibre density -IENFD- at proximal and distal site. Green colour represents patients who followed physical exercise. Patients with less compromised nerves epidermal density who observed regular physical activity showed lower levels of fatigue at follow-up.

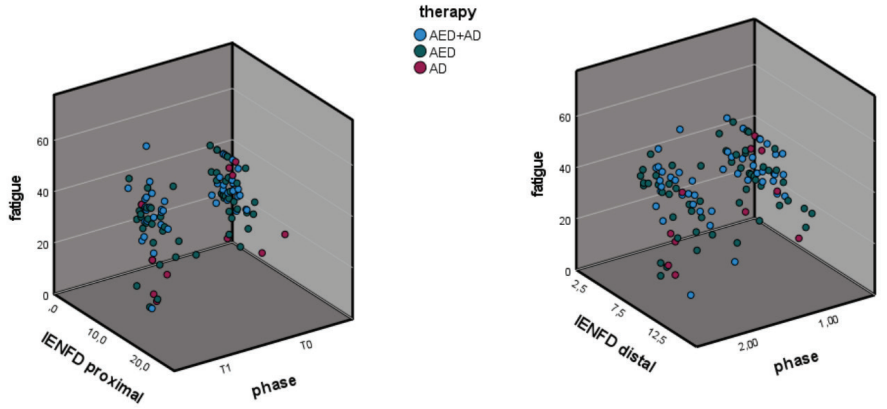

Fig. 7. Outcome of fatigue in relation to intraepidermal nerve fibre density -IENFD- at proximal and distal site. Colour represents patients treated with monotherapy or combined therapy (in light blue) followed physical exercise. Patients with combined therapy showed high levels of fatigue (Bonferroni AED+AD *vs*. AD, *p* 0.035; AED+AD *vs*. AED, *p* 0.003) and less improvement at follow-up. This trend was more evident in patients with small fibre denervation at distal and proximal sites.

validity linked to pain was a natural evolution of disease, or it was an effect of treatments, as we have not a control group. Furthermore, most of the patients assumed AED, alone or in association with AD, so a reliable comparison between the two types of drugs is not computable. The reduction of disability linked to pain as measured with BPI-Pain, and of DN4 scores, could be an effect of AED and AD, indicated for the treatment of neuropathic pain (33). As could be expected, patients under combined treatment had a global more severe clinical profile, especially for fatigue, that showed also a weaker improvement at follow-up. Anyway, the large number of patients lost to follow-up for several reasons as scarce compliance, impression of low benefit and side effects, confirm previous data on large populations (34). In fact, clinicians prescribed drugs according to the most reliable evidence of efficacy (20), but non pharmacological approach in site of pharmacological treatments are generally recommended (34). Unfortunately, non-pharmacological treatments are difficult to be applied in our public hospitals, and drugs remain the main choice, together with the programme of physical exercise. We can presently suggest that the presence of small fibre sufferance could have an effect on the response to different treatments, in particular influencing a minor benefit on fatigue in non-responder patients, who were suggested to take combined treatment. As regard to physical exercise, it seemed to ameliorate clinical picture in the FM group. However, this beneficial effect was limited to the fatigue. The modality of physical activity execution could be responsible for the lack of relevant effect on the global disability. Patients were not followed by expert trainers during the motor programming, so the modality they executed the activity is uncertain. The lack of a constant supervision on the physical exercise performance could also facilitate the renounce to cooperate with the programme. In fact, patients with normal IENFD had a better clinical effect with physical exercise, with a particular improvement in fatigue. Patients with reduced IENFD could have more problems with movement (6) and could request on person tailored physical activity programmes.

Study limitation

This is an observational real-life study, with limited reliability in regard to effect of treatments and compliance with physical activity programme, given the lack of a control non treated group, a

system for aerobic exercise execution monitoring and the paucity of cases in single treatment groups. Most of the patients presented with IENFD reduction at proximal site, while groups with normal or reduced nerve density were small and of limited statistic reliability.

Conclusions

The results of this observational real-life follow-up study suggest that small fibre impairment in FM is stable in medium term. However, the reduction of IENFD together with fatigue and invalidity linked to motor performances, seem indicators of worse disability evolution. A possible influence of small fibre dysfunction on motor performance could thus have a role in FM evolution.

Though we cannot at present give a general impression of possible influence of small fibre pathology on drugs efficacy, it seems that the beneficial effect of physical exercise could be limited in patients with reduced IENFD. In person tailored physical exercise programmes with expert trainer supervision could be a choice for those patients.

References

1. WOLFE F, CLAUW DJ, FITZCHARLES MA *et al*.: Revisions to the 2010/2011 fibromyalgia diagnostic criteria. *Semin Arthritis Rheum* 2016; 46: 319-29. https://doi.org/10.1016/j.semarthrit.2016.08.012
2. YUNUS MB: Editorial review: an update on central sensitivity syndromes and the issues of nosology and psychobiology. *Curr Rheumatol Rev* 2015; 11: 70-85. https://doi.org/10.2174/1573397111102150702112236
3. METYAS S, CHEN C, QUISMORIO A, ABDO N, KAMEL K: Improvement of nerve fiber density in fibromyalgia patients treated with IVIg. *Curr Rheumatol Rev* 2020; 16: 280-4. https://doi.org/10.2174/1573397115666191106120622
4. NOLANO M, TOZZA S, CAPORASO G, PROVITERA V: Contribution of Skin Biopsy in Peripheral Neuropathies. *Brain Sci* 2020; 10: 989. https://doi.org/10.3390/brainsci10120989
5. DI CARLO M, CESARONI P, SALAFFI F: Neuropathic pain features suggestive of small fibre neuropathy in fibromyalgia syndrome: a clinical and ultrasonographic study on female patients. *Clin Exp Rheumatol* 2021; 39 (Suppl. 130): S102-7. https://doi.org/10.55563/clinexprheumatol/r0kho4
6. VECCHIO E, LOMBARDI R, PAOLINI M *et al*.: Peripheral and central nervous system correlates in fibromyalgia. *Eur J Pain* 2020; 24: 1537-47. https://doi.org/10.1002/ejp.1607
7. FASOLINO A, DI STEFANO G, LEONE C *et al*.: Small-fibre pathology has no impact on somatosensory system function in patients with fibromyalgia. *Pain* 2020; 161: 2385-93. https://doi.org/10.1097/j.pain.0000000000001920
8. EVDOKIMOV D, FRANK J, KLITSCH A *et al*.: Reduction of skin innervation is associated with a severe fibromyalgia phenotype. *Ann Neurol* 2019; 86: 504-16. https://doi.org/10.1002/ana.25565
9. BERGENHEIM A, JUHLIN S, NORDEMAN L, JOELSSON M, MANNERKORPI K: Stress levels predict substantial improvement in pain intensity after 10 to 12 years in women with fibromyalgia and chronic widespread pain: a cohort study. *BMC Rheumatol* 2019; 3: 5. https://doi.org/10.1186/s41927-019-0072-9
10. BODÉRÉ C, CABON M, WODA A *et al*.: A training program for fibromyalgia management: A 5-year pilot study. *SAGE Open Med* 2020; 8: 2050312120943072. https://doi.org/10.1177/2050312120943072
11. SANTOS E CAMPOS MA, PÁRRAGA-MONTILLA JA, ARAGÓN-VELA J, LATORRE-ROMÁN PA: Effects of a functional training program in patients with fibromyalgia: A 9-year prospective longitudinal cohort study. *Scand J Med Sci Sports* 2020; 30: 904-13. https://doi.org/10.1111/sms.13640
12. WOLFE F, CLAUW DJ, FITZCHARLES MA *et al*.: The American College of Rheumatology preliminary diagnostic criteria for fibromyalgia and measurement of symptom severity. *Arthritis Care Res* (Hoboken) 2010; 62: 600-10. https://doi.org/10.1002/acr.20140
13. JOHNSON EW: Visual analog scale (VAS). *Am J Phys Med Rehabil* 2001; 80: 717. https://doi.org/10.1097/00002060-200110000-00001
14. ZUNG WW: A self-rating depression scale. *Arch Gen Psychiatry* 1965; 12: 63-70. https://doi.org/10.1001/archpsyc.1965.01720310065008
15. ZUNG WW: A rating instrument for anxiety disorders. *Psychosomatics* 1971; 12: 371-9. https://doi.org/10.1016/s0033-3182(71)71479-0
16. BIDARI A, HASSANZADEH M, MOHABAT MF, TALACHIAN E, KHOEI EM: Validation of a Persian version of the Fibromyalgia Impact Questionnaire (FIQ-P). *Rheumatol Int* 2014; 34: 181-9. https://doi.org/10.1007/s00296-013-2883-0
17. BOUHASSIRA D, ATTAL N, ALCHAAR H *et al*.: Comparison of pain syndromes associated with nervous or somatic lesions and development of a new neuropathic pain diagnostic questionnaire (DN4). *Pain* 2005; 114: 29-36. https://doi.org/10.1016/j.pain.2004.12.010
18. BELZA B, MIYAWAKI CE, LIU M *et al*.: A systematic review of studies using the Multidimensional Assessment of Fatigue Scale. *J Nurs Meas* 2018; 26: 36-75. https://doi.org/10.1891/1061-3749.26.1.36
19. CARACENI A, MENDOZA TR, MENCAGLIA E *et al*.: A validation study of an Italian version of the Brief Pain Inventory (Breve Questionario per la Valutazione del Dolore). *Pain* 1996; 65: 87-92. https://doi.org/10.1016/0304-3959(95)00156-5
20. MACFARLANE GJ, KRONISCH C, DEAN LE *et al*.: EULAR revised recommendations for the management of fibromyalgia. *Ann Rheum Dis* 2017; 76: 318-28. https://doi.org/10.1136/annrheumdis-2016-209724
21. VECCHIO E, QUITADAMO SG, RICCI K *et al*.: Laser evoked potentials in fibromyalgia with peripheral small fiber involvement. *Clin Neurophysiol* 2022; 135: 96-106. https://doi.org/10.1016/j.clinph.2022.01.001
22. DEVIGILI G, TUGNOLI V, PENZA P *et al*.: The diagnostic criteria for small fibre neuropathy: from symptoms to neuropathology. *Brain* 2008; 131(Pt 7): 1912-25. https://doi.org/10.1093/brain/awn093
23. LAURIA G, HSIEH ST, JOHANSSON O *et al*.: European Federation of Neurological Societies; Peripheral Nerve Society. European Federation of Neurological Societies/Peripheral Nerve Society Guideline on the use of skin biopsy in the diagnosis of small fiber neuropathy. Report of a joint task force of the European Federation of Neurological Societies and the Peripheral Nerve Society. *Eur J Neurol* 2010; 17: 903-12. https://doi.org/10.1111/j.1468-1331.2010.03023.x
24. LAURIA G, BAKKERS M, SCHMITZ C *et al*.: Intraepidermal nerve fiber density at the distal leg: a worldwide normative reference study. *J Peripher Nerv Syst* 2010; 15: 202-7. https://doi.org/10.1111/j.1529-8027.2010.00271.x
25. DE TOMMASO M, VECCHIO E, NOLANO M: The puzzle of fibromyalgia between central sensitization syndrome and small fiber neuropathy: a narrative review on neurophysiological and morphological evidence. *Neurol Sci* 2022; 43: 1667-84. https://doi.org/10.1007/s10072-021-05806-x
26. KHOSHNOODI MA, TRUELOVE S, BURAK-GAZI A, HOKE A, MAMMEN AL, POLYDEFKIS M: Longitudinal assessment of small fiber neuropathy: evidence of a non-length-dependent distal axonopathy. *JAMA Neurol* 2016; 73: 684-90. https://doi.org/10.1001/jamaneurol.2016.0057
27. JOHNSON SA, SHOUMAN K, SHELLY S *et al*.: Small fiber neuropathy incidence, prevalence, longitudinal impairments, and disability. *Neurology* 2021; 97: e2236-e2247. https://doi.org/10.1212/wnl.0000000000012894
28. WOLFE F, ABLIN J, BAKER JF, DIAB R *et al*.: All-cause and cause-specific mortality in persons with fibromyalgia and widespread pain: An observational study in 35,248 persons with rheumatoid arthritis, non-inflammatory rheumatic disorders and clinical fibromyalgia. *Semin Arthritis Rheum* 2020; 50: 1457-64. https://doi.org/10.1016/j.semarthrit.2020.02.005
29. CORRÀ MF, VILA-CHÃ N, SARDOEIRA A *et al*.: Peripheral neuropathy in Parkinson's disease: prevalence and functional impact on gait and balance. *Brain* 2023; 146: 225-36. https://doi.org/10.1093/brain/awac026
30. GENTILE E, RICCI K, DELUSSI M, BRIGHINA F, DE TOMMASO M: Motor cortex function in fibromyalgia: a study by functional near-infrared spectroscopy. *Pain Res Treat* 2019; 2019: 2623161. https://doi.org/10.1155/2019/2623161
31. GENTILE E, BRUNETTI A, RICCI K *et al*.: Mutual interaction between motor cortex activation and pain in fibromyalgia: EEG-

fNIRS study. *PLoS One* 2020; 15: e0228158. https://doi.org/10.1371/journal.pone.0228158
32. GENTILE E, BRUNETTI A, RICCI K, BEVILACQUA V, CRAIGHERO L, DE TOMMASO M: Movement observation activates motor cortex in fibromyalgia patients: a fNIRS study. *Sci Rep* 2022; 12: 4707. https://doi.org/10.1038/s41598-022-08578-2
33. MOISSET X, PAGE MG, PEREIRA B, CHOINIERE M: Pharmacological treatments of neuropathic pain: real-life comparisons using propensity score matching. *Pain* 2022; 163: 964-74. https://doi.org/10.1097/j.pain.0000000000002461
34. SARZI-PUTTINI P, GIORGI V, MAROTTO D, ATZENI F: Fibromyalgia: an update on clinical characteristics, aetiopathogenesis and treatment. *Nat Rev Rheumatol* 2020; 16: 645-60. https://doi.org/10.1038/s41584-020-00506-w