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Research Article

Quantification of Progressive Retinal Thinning In Patients with Fibromyalgia Syndrome over a Period of 5 Years

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Abstract

Purpose: To quantify changes in visual function parameters and the macular neuroretina of patients with Fibromyalgia (FM) over 5 years, compared with controls.

Methods: Eighty patients with FM and 38 healthy subjects were included in a prospective observational study and underwent visual acuity (VA) evaluation with ETDRS chart, contrast sensitivity vision (CSV) with CSV 1000E test, and retinal evaluation using Spectralis Optical coherence tomography (OCT). All subjects were re-evaluated after 5 years to quantify changes in visual function parameters and ganglion cell layer (GCL) and retinal nerve fiber layer (RNFL) thickness. The relationship between progressive structural, functional and disease severity changes was analysed. Additionally, patients were classified into three different groups to analyse progression depending on the disease phenotype.

Results: When compared with controls, patients with FM presented worse low contrast VA ($p=0.024$), and low frequency CSV ($p=0.004$) after a 5-year follow up. A progressive decrease affecting the GCL thickness (nasal 1, $p=0.004$; temporal 1, $p<0.001$; inferior 1, $p=0.001$) and the RNFL (nasal 1 and 2, $p<0.001$; superior 1, $p<0.001$; and inferior 1, $p=0.002$) was observed in patients over the monitoring time. Changes affecting the GCL were correlated with progression in disease severity scores (EQ-5D, $r=0.560$, $p<0.001$; FIQ, $r=-0.470$, $p=0.003$). Correlations between structural changes and disease severity scores were only observed in the atypical and biologic phenotypes.

Conclusions: Progressive visual dysfunction and retinal neurodegeneration was detected in FM patients. The evaluation of visual parameters and GCL/RNFL thickness using SD-OCT can be useful to monitor FM progression.

INTRODUCTION

Fibromyalgia (FM) presents widespread pain and generalized hyperalgesia for mechanical pressure (1). It affects approximately a 2% the world population and it is also called chronic pain syndrome or chronic fatigue syndrome (1,2). These patients' quality of life experiences from mild to severe affectation (1-3).

Some theories nowadays suggest that the clinical presentation of FM is determined by central phenomena instead of peripheral dysfunction; nevertheless, the pathophysiology is not entirely comprehended. It has been suggested an implication of a possible imbalance of inflammatory biomarkers (4). Furthermore, patients with FM syndrome have been reported to experience changes in brain perfusion, structure and functional responses to pain (5-7).

In recent years, Multiple sclerosis, Parkinson disease or Alzheimer are examples of neurodegenerative processes in which the retinal ganglion cell layer (GCL) has been recognized as a useful biomarker for diagnosis and monitoring of such diseases (8-11). Moreover, other mental disorders (such as schizophrenia and bipolar syndrome) also presented retinal neurodegeneration, providing new information of the pathophysiology of psychiatric diseases (12-14). Observable/visible retinal changes were recently appreciated/found to be present in FM by optical coherence tomography (OCT) (15), increasing the number of neurologic syndromes with a possible neurodegenerative course underneath what is known to its pathophysiology nowadays.

Supervising retinal and visual changes over time in individuals with neurodegenerative processes is of a great relevance: it contributes to a further understanding of the annual

neurodegeneration rate, provide clinicians with a biomarker of progression and even of prognosis, and permits to evaluate the effectivity of different treatments (16,17). Progressive visual dysfunction and neuroretinal degeneration in patients with FM were evaluated over a period of 5 years in the present study. Very little literature on ophthalmological changes in FM syndrome has been written, and to date, this is the first longitudinal study with the objective of assessing progressive changes in these patients.

METHODS

Some of the procedures described in this document were detailed elsewhere (15,17). Confirmed FM patients were incorporated into this prospective longitudinal study with a follow-up of 5 years. A power calculation was performed, based in the results of our previous studies and assuming an alpha error of 5% and a beta error of 10%. A standard sample size equation was used to calculate the number of subjects required, that was 37 in each group (FM patients and healthy controls). To further increase the power of the study, we included more FM patients. Finally, 80 suitable individuals were included in the study and sex and age-matched with 38 healthy controls. Both groups were evaluated at baseline (recruitment and data collection: 2015) and at 5 years (re-evaluation and data collection/analysis: 2020). All procedures adhered to the tenets of the Declaration of Helsinki and all participants provided written informed consent to participate in the study.

Patients were selected from the Primary Care Research Group Study population of FM patients in Zaragoza, Spain. This research group provided all patients that were included in the first cohort in 2015 and results of the cross-sectional study have been published elsewhere (15). FM diagnosis was based on the 1990 American College of Rheumatology criteria for FM (18). A specializing FM psychiatrist, who evaluated the patients and was blind to the ophthalmology assessment recorded type of FM, disease duration, age at diagnosis and treatment. Severity of FM was established using the Fibromyalgia Impact Questionnaire (FIQ); and evaluation of activities of daily living and impact on quality of life using the Euro Quality of Life 5D (EQ-5D) scale. The ophthalmologic evaluation consisted of anterior segment assessment, best-corrected visual acuity based on the Snellen scale, visual field test, OCT evaluation, and a funduscopic exam. All individuals were evaluated by two neuro-ophthalmologists who were blind to the psychiatrist evaluation. The exclusion criteria consisted of: patients with BCVA lower than 0.4 (decimal, measured with Snellen chart), significant refractive errors (>5 diopters of spherical equivalent refraction or 3 diopters of astigmatism), intraocular pressure ≥21 mmHg, media opacifications, concomitant ocular diseases (including history of glaucoma or retinal pathology) and systemic conditions (especially neurodegenerative processes) that could affect the visual system. No history and no evidence of ocular or neurologic disease of any nature had been previously observed in healthy controls; their best-corrected visual acuity (BCVA) was >0.4. Each eye was considered independently and only one eye of each subject was randomly included unless only one of the eyes met the exclusion criteria.

Visual Function Evaluation

Visual function was tested by assessing photopic BCVA and contrast sensitivity vision (CSV). BCVA was evaluated using an ETDRS chart at two different contrast levels: 100% (High contrast VA [HCVA], using ETDRS chart) and 2.50%, (Low contrast VA [LCVA], using Low-Contrast ETDRS chart). We obtained all measurements under monocular vision and controlled lighting conditions with best correction. Results were recorded in LogMar. CSV, which offers more precise data about the visual pathway than BCVA, was evaluated using the CSV 1000E test. This test evaluates contrast sensitivity at 4 different spatial frequencies (3, 6, 12, and 18 cycles per degree [cpd]). The chart comprises four rows with 17 circular patches each. The patches present a grating that decreases in contrast moving from left to right across the row. The subject has to indicate whether the grating appears in the top patch or the bottom patch for each column. Each contrast value for each spatial frequency was transformed into a logarithmic scale according to standardized values. All patients were evaluated at a distance of 2.5 meters from the chart under monocular vision

Macular Structural Evaluation

Structural measurements of the retina were obtained using the Spectralis OCT device (Heidelberg Engineering, Germany). Retinal segmentation was performed using the fast macular protocol for Spectralis OCT to identify the RNFL and the GCL and to quantify its thickness. Signal strength is indicated by a blue quality bar in the image (range is 0-40, where 0 is categorized as poor quality and 40 as excellent). We included images with a score higher than 25 in the analyses. Adhering to the suggested procedure, the subject's pupil was first centered and focused on an iris viewing camera, and then the device's image calibrating system was used to optimize the retina visualization. Once the saturation and placement of the scan was optimal, we always activated the Automatic Real-time Tracking (ART) and maintained the image quality using the smaller live image screen at the bottom of the monitor. The device obtained perifoveal retinal scans comprising 25 single horizontal axial scans in a scanning area of 666 square mm. Registered parameters included the 9 ETDRS macular areas, which are displayed as superior 1, nasal 1, inferior 1 and temporal 1, corresponding to the inner ring; and superior 2, nasal 2, inferior 2 and temporal 2, corresponding to the outer ring. Additionally, average central thickness and foveal (center) thickness were recorded.

Fibromyalgia Evaluation

A specialized psychiatrist evaluated all the patients and classified them following FM subgrouping at the Miguel Servet Hospital Fibromyalgia Unit, based on the pressure-pain thresholds and psychologic factors described by Giesecke et al (19). The Giesecke classification includes three subgroups of FM: Subgroup1 (atypical): low tenderness, moderate depression/anxiety, moderate catastrophizing, and moderate control over pain; Subgroup 2 (depressive): high tenderness, high depression/anxiety, high catastrophizing, and low control over pain; and Subgroup 3 (biologic): high tenderness, low depression/anxiety, low catastrophizing, and high control over pain.

Additionally, each subject with FM also completed the FIQ and the EQ-5D questionnaire, to check the impact of the disease and the quality of life and activities of daily living respectively.

The approved Spanish form of these questionnaires was used (20,21). For the FIQ, patients were assigned a score from 0 to 100. The higher the score, the greater the disease impact. The EQ-5D comprises five questions with three response categories concerning the following dimensions: mobility, self-care, usual activities, pain, and anxiety/depression. The EQ-5D results are expressed as a percentage from 0 to 100, being 100 the best health status possible, and 0 the worst status possible in these patients (22).

Statistical Analysis

All subjects were evaluated after 5 years from baseline (2020 and 2015, respectively), and the 5-year change per subject on each variable was calculated. Modifier variables were age, sex, and intraocular pressure. Statistical analysis was performed using commercial predictive analytics software (SPSS, version 20.0; SPSS, Inc., Chicago, IL). The normality of the sample distribution was assessed using the Kolmogorov-Smirnov test. Since most variables did not follow normal distribution non-parametric tests were performed for calculations. FM disease scores, and visual function and GCL thickness parameters were compared between baseline and the 5-year visit using the Wilcoxon test for paired data. Changes registered during the follow-up were calculated for each subject in every variable and were compared between FM patients and healthy controls using Mann Whitney's U test. A p value of <0.05 was considered statistically significant; however, Bonferroni correction for multiple comparisons was applied to avoid bias (see tables).

An additional analysis in FM phenotypes was performed: changes observed in the different FM phenotypes were compared between subgroups using the ANOVA and Post hoc analysis, to analyze whether any subgroup presented greater change in time compared to the other subgroups.

Possible associations between structural and functional changes and FM parameters (type of FM, impact of disease and EQ-5D score) were analyzed by means of Spearman's correlation Test.

RESULTS

Eighty eyes of 80 patients and 38 eyes of 38 healthy individuals were included in this longitudinal study. Age, sex, and intraocular pressure did not differ significantly between the groups, nor at baseline or at 5-year follow up. Mean disease duration at 5 years was 12.84±3.95 years. The FM phenotype distribution was: biologic FM, 18 patients (22.50%); depressive FM, 22 patients (27.5%); atypical FM, 40 patients (50%). The FIQ mean score at baseline was 61.05±19.57 and 64.85±19.39 at 5-year follow up (p=0.458). The EQ-5D mean score was 44.38±18.63 at baseline, and 39.78±16.48 at 5-year follow up (p=0.03). (All demographic variables and significance are included in (Table 1).

After 5 years, patients with FM presented significantly worse visual function outcomes compared to baseline affecting CSV in all 4 spatial frequencies (Table 2). BCVA (at 100% and 2.50% contrast) did not change significantly over time. Healthy controls did not present significant changes over time (Table 2) in any of the visual function variables.

Table 1: Demographic data of patients and controls included in the study, at baseline and at 5-year follow up. Bold numbers indicate statistical significance.

Variable	FM	Controls	p
Age			
baseline	51.98±8.08	49.50±9.75	0.151
5 year	56.51±8.13	59.35±6.92	0.223
Sex M/F %			
baseline	4.9/95.1	16.7/83.3	0.255
5 year	5.1/94.9	13.9/77.8	0.330
IOP			
baseline	13.22±2.33	13.95±3.56	0.399
5 year	13.88±3.08	14.02±2.97	0.219
Age at diagnosis	43.44±8.35		
Disease phenotype			
Atypical	18		
Depressive	22		
Biologic	40		
baseline	7.80±4.60		
5 year	12.84±3.95		
Eq5d score			
baseline	44.38±18.63		**0.030**
5 year	39.78±16.48		
FIQ score			
baseline	61.05±19.57		0.458
5 year	64.85±19.39		

When we compared the 5-year change between patients and controls, patients presented greater change (worse) in low contrast BCVA (p=0.024) and CSV affecting low frequencies (3 cpd, p=0.004; 6 cpd, p=0.004) compared to controls (Table 2).

A significant reduction of the macular GCL was observed in patients after 5 years, affecting the nasal (N1, p=0.004), temporal (T1, p<0.001) and inferior (I1, p=0.001) quadrants (Table 3). Additionally, there was a significant reduction of the RNFL in the nasal (N1, p<0.001; N2, p<0.001), superior (S1, p<0.001; S2, p<0.001) and inferior (I1, p=0.002) quadrants. Healthy controls did not present any significant changes in macular measurements over time (table 3). No significant differences were observed between patients and controls when the 5-year change in structural measurements was compared.

Changes Based on Fibromyalgia Phenotype

All patients were divided into three different groups based on their FM phenotype (subgroup 1: atypical; subgroup 2: depressive; subgroup 3: biologic) and differences in the 5-year change between groups were calculated using ANOVA test and post hoc analysis. Statistical differences between the different phenotypes were only observed in the CSV results, affecting the spatial frequency of 12 cpd (high frequency) (ANOVA p=0.019). Post hoc analysis revealed that the atypical phenotype (subgroup 1) presented worse CSV at 12 cpd over time compared to the

Table 2: Visual function parameters in patients with fibromyalgia and healthy controls, at baseline and 5-year follow up. P* indicates comparison between data from baseline and 5 years in each group, using Wilcoxon test (paired data). Change was calculated for each variable in each patient. P indicates comparison between changes observed in patients and controls, calculated by Mann whitney's U test. Bold numbers indicate significance according to Bonferroni's test for multiple comparisons. Significance value based on Bonferroni correction for multiple comparisons: VA EDTRS, 0.025; CSV1000E, 0.0125.

Variable	FM baseline	FM 5 year	Change	P*	Healthy baseline	Healthy 5 years	change	P*	P
VA 100	0.04±0.18	0.01±0.17	-0.03±0.22	0.448	0.05±0.07	-0.06±0.11	-0.17±0.11	0.039	0.029
VA 2.50	0.30±0.13	0.34±0.19	0.03±0.18	0.258	0.39±0.10	0.35±0.14	-0.18±0.08	0.109	**0.024**
CSV 3 cpd	1.74±0.15	1.58±0.15	-0.18±0.16	**<0.001**	1.64±0.12	5.15±1.28	3.35±0.95	0.109	**0.004**
CSV 6 cpd	1.91±0.17	1.79±0.14	-0.11±0.18	**0.002**	1.71±0.19	5.00±1.87	2.95±2.00	0.109	**0.004**
CSV 12 cpd	1.53±0.25	1.29±0.27	-0.23±0.25	**<0.001**	1.410.14±	4.00±2.12	1.25±1.98	0.285	0.089
CSV 18 cpd	1.02±0.26	0.85±0.17	-0.15±0.28	**0.009**	1.16±0.24	4.15±2.23	1.83±2.24	0.285	0.175

Table 3: Retinal structural parameters in patients with fibromyalgia and healthy controls, at baseline and 5-year follow up. P* indicates comparison between data from baseline and 5 years in each group, using Wilcoxon test (paired data). Change was calculated for each variable in each patient. P indicates comparison between changes observed in patients and controls, calculated by Mann whitney's U test. Bold numbers indicate significance according to Bonferroni's test for multiple comparisons. Abbreviations: Min, minimum; FM, fibromyalgia; GCL, ganglion cell layer; IPL, inner plexiform layer.

Variable	FM baseline	FM 5 year	Change	P*	Healthy baseline	Healthy 5 year	Change	P*	P
GCL									
Average central	16.22±4.22	16.40±5.14	0.13±3.12	0.591	15.58±2.85	16.40±4.28	0.57±4.14	0.750	0.993
Nasal 1	51.24±5.79	48.48±6.96	-1.52±3.34	**0.004**	50.42±3.93	50.23±5.28	-0.57±3.06	0.185	0.272
Nasal 2	37.41±4.00	36.83±4.39	0.28±1.97	0.446	36.95±3.59	38.13±4.53	0.89±1.88	0.057	0.335
Superior 1	50.78±5.85	49.64±5.47	-0.39±2.03	0.116	51.53±4.81	51.83±5.69	-0.26±2.74	0.320	0.925
Superior 2	35.54±4.10	34.03±4.27	-0.28±1.33	0.162	34.53±3.27	35.97±3.81	1.15±2.16	0.037	0.007
Temporal 1	45.93±4.82	44.01±5.68	-1.86±3.28	**<0.001**	45.58±4.65	46.00±5.56	-0.10±3.12	0.913	0.073
Temporal 2	34.48±4.28	33.76±4.89	-0.21±2.50	0.255	34.89±4.42	35.83±4.28	0.63±2.47	0.289	0.158
Inferior 1	51.57±5.11	49.10±6.70	-1.47±3.94	**0.001**	51.32±4.36	51.37±5.34	-0.94±1.54	0.020	0.743
Inferior 2	31.72±3.51	30.58±3.98	-0.78±1.94	0.006	32.42±3.59	32.57±4.08	0.36±1.97	0.464	0.025
Center	4.88±3.48	6.11±3.59	1.27±3.14	0.022	3.42±2.26	5.37±4.10	1.94±4.36	0.040	0.869
RNFL									
Average central	12.92±2.13	12.38±2.26	-0.32±1.57	0.175	13.20±1.87	12.79±3.38	0.20±4.49	0.496	0.521
Nasal 1	22.12±2.21	21.57±6.80	-1.85±2.28	**<0.001**	20.40±1.95	20.13±3.61	-0.70±4.29	0.147	0.556
Nasal 2	52.60±9.35	48.82±11.19	-2.97±4.11	**<0.001**	47.30±14.44	44.33±13.03	-3.80±13.58	0.192	0.893
Superior 1	23.80±2.84	23.05±3.73	-1.20±1.97	**<0.001**	24.50±3.10	24.46±5.52	0.80±7.16	0.766	0.410
Superior 2	37.96±6.13	36.77±6.46	-1.35±3.43	0.010	38.40±6.46	38.13±5.54	-1.00±5.03	0.497	0.951
Temporal 1	18.12±1.27	18.34±3.54	-0.62±1.68	0.030	18.40±2.45	18.38±3.53	-0.30±1.25	0.417	0.584
Temporal 2	19.52±1.98	19.87±4.04	-0.52±1.46	0.020	21.80±9.07	23.79±11.20	3.40±9.52	0.340	0.067
Inferior 1	27.24±3.66	25.90±4.50	-1.60±2.87	**0.002**	23.60±3.62	24.96±4.01	-0.40±1.95	0.495	0.220
Inferior 2	42.84±10.12	41.57±11.61	-0.50±4.58	0.381	40.70±9.65	38.04±6.82	-2.80±4.70	0.084	0.119
Center	1.95±3.49	3.58±4.93	1.72±4.80	0.017	2.88±3.64	4.06±4.29	2.00±5.50	0.461	0.778

depressive phenotype (p=0.019) but this reduction was not significant when compared to the biologic phenotype (p=0.139). Change over time in disease severity parameters and structural variables was not significantly different between the FM phenotypes (These data are not shown in tables, data concerning the ANOVA-Post hoc analysis will be provided upon request to the corresponding author).

Correlations

The correlation between the 5-year change in the FM scores and functional /structural parameters was calculated using the Spearman Rho test. A strong inverse correlation between the 5-year change in the EQ-5D score and the FIQ results (r=-0.700, p<0.001) was observed.

A moderate correlation was observed between progressive thinning in the central average thickness of the GCL and progression of disease severity as measured with the EQ-5D score (r=0.560, p=0.001) and the FIQ (r= -0.470, p=0.003). Additionally, progressive thinning of the RNFL was associated with worsening of LCVA (these results can be observed in table 4).

When correlations were calculated based on FM phenotypes, the atypical phenotype (subgroup 1) presented important correlations between a higher number of variables than any of the other subgroups. Change in the EQ-5D score was associated with changes in the FIQ (r= -0.64, p=0.006), and similar to what was observed in the total FM group, progressive thinning of the GCL (average central) was significantly correlated with the EQ-5D score (r=0.675, p= 0.032) and the FIQ score (r=-0.665, p=0.032).

Changes in the average central thickness of the GCL were also strongly correlated with worsening of the EQ-5D score in the biologic phenotype (r=0.708, p= 0.001).

Changes in the EQ-5D score over the 5-year period were strongly correlated with changes in the FIQ results in all three FM phenotypes; however, the depressive phenotype presented the strongest correlation (r=-0.84, p=<0.001).

Significant correlations found in the different FM phenotypes can be seen in table 5. Non-significant data do not appear in the tables.

DISCUSSION

To our knowledge, this is the first longitudinal study assessing progressive changes in the functional and retinal parameters of patients suffering from FM. At the end of 5 years, our patients presented progressive CSV loss and progressive retinal thinning affecting the macular area. GCL thickness was found to be remarkably reduced in our patients after 5 years, particularly affecting the nasal, temporal and inferior quadrants. The RNFL was also reduced in our patients; moreover, we found significant thinning slightly affecting more areas than the GCL, suggesting that the progressive change observed in the neuroretina of these patients might not be local (i.e. not primarily affecting the ganglion cells) but retrograde damage from neurodegeneration occurring in the central nervous system. The retina (specially the neuroretina, composed by the GCL complex and their axons) is a window to the central nervous system, axonal loss secondary to neurodegenerative processes such as multiple sclerosis or Parkinson disease has been priory detected by OCT measurements of the inner retinal layers (8, 9, 24). Nevertheless, whether damage can be observed earlier in the GCL or the RNFL is still controversial depending on the disease and published series. Most studies on multiple sclerosis point to the GCL as the most sensitive biomarker for neurodegeneration (25,26). Our current results suggest that neurodegeneration is present in FM patients and causes progressive thinning on the GCL and the RNFL of the macular area. More studies are needed to corroborate our findings and to elucidate whether the RNFL might be a more sensitive biomarker than the GCL for monitoring disease progression in these patients.

Scarce literature on retinal degeneration in FM patients is available. We could not find any published research into axonal loss in FM other than our earlier cross-sectional results, which showed RNFL loss in the peripapillary area and a tendency towards GCL loss in the macular zone (15). Investigation on retinal perfusion in FM patients is also almost inexistent (27,28). Bambo et al evaluated perfusion at the optic nerve head of FM patients using colorimetric analysis software and observed that hemoglobin levels were reduced in patients with FM, particularly within the neuro-retinal rim. Nevertheless, the macular area was not evaluated. (28) contributed to new insights to the pathophysiology of this syndrome by detecting choroidal thinning in the macular area of FM patients. This decline in blood perfusion was suggested to be related to changes in autonomic nervous system functioning.

Table 4: Significant associations found between structural parameters and functional parameters in patients with FM syndrome.

Structural parameter	Functional parameter	R	P
CL avg central	EQ5D	0.560	<0.001
	FIQ	-0.470	0.003
RNFL Nasal 1	VA ETDRS 2.50	-0.408	0.009
RNFL Nasal 2	VA ETDRS 2.50	-0.560	<0.001
RNFL Inferior 1	VA ETDRS 2.50	-0.400	0.011

Table 5: Significant associations found in the different fibromyalgia phenotypes.

FM phenotype	Variables associated	R	P
Atypical	EQ5D - FIQ	-0.64	0.006
	EQ5D –GCL avg central	0.675	0.032
	FIQ - GCL avg central	-0.665	0.036
	RNFL nasal 2 – ETDRS 2.50	-0.740	0.036
Depressive	Eq5D - FIQ	-0.84	<0.001
Biologic	Eq5D - FIQ	-0.80	<0.001
	EQ5D-GCL avg central	0.708	0.001
	RNFL inferior 2- ETDRS 2.50	-0.513	0.021

Nowadays, views of the etiology of FM indicate an involvement of central phenomena with the central nervous system playing a leading role (29). Some abnormalities in sensory signaling which have also been proved to be related to central sensitization in these patients include changes in key neurotransmitters and reduction of descending control (30). Moreover, there are possible altered pain pathways present as abnormal amplifications of pain in FM patients (31,32) and a chronic pro-inflammatory state (both in the CNS and in peripheral tissues). Nonetheless, theories explaining retinal thinning in FM syndrome are scarce. Earlier investigations described neurobiologic and brain structure irregularities in these patients (1,7). Clauw et al reported a central sensitization in FM provoked by neurobiologic abnormalities. Our previous findings support this theory and suggest that neurodegeneration is causing RNFL depletion and contributing to the pathology of FM. The theory of neurodegeneration causing RFNL depletion and contributing to the pathology of FM is suggested and supported by our previous discoveries.

However, basing on Bambo et al and Ulusoy et al research, progressive retinal thinning could also be caused by alterations in ocular perfusion in these subjects. Earlier studies on FM syndrome found hypoperfusion (both central and peripheric) as the most important factor in the origin of chronic abnormal pain in these subjects (33-35). As the choroid irrigates only the external retinal layers, more studies on retinal blood flow are still needed in these patients to analyze whether a decrease in the irrigation of the retinal internal layers (neuroretina) exists and to determine a possible correlation between GCL thinning and retinal vascularization changes.

An important finding in our study is the significant correlation observed between disease severity progression, as measured with the EQ-5D scale and the FIQ, and progressive thinning of the GCL (central average thickness). Currently, there are no specific nor definitive diagnostic tests for FM syndrome. Our results provide a new option not only to facilitate the diagnosis of FM but also to monitor disease progression. The ability to evaluate the retinal ganglion cells as an indicator of disease progression is an important advance, and this examination can be easily implemented in clinical practice, because OCT tests are noninvasive, fast, and comfortable for patients, as well as inexpensive.

Another important finding in our study concerns results observed by disease phenotype. There were no differences in the 5-year change of the EQ-5D score between the three FM phenotypes (meaning, no phenotype worsened more than the others during the 5-year period) and no differences concerning GCL loss. However, the atypical phenotype presented worse CSV (affecting a specific spatial frequency) than the depressive phenotype. Despite no differences could be found between the other groups affecting this functional parameter, it might help orientate diagnosis when other diagnostic tests are insufficient to stablish a definite diagnosis on a specific phenotype.

Additionally, both the atypical and the biologic phenotypes presented a strong correlation between disease severity scores and progressive thinning affecting the average central thickness of the GCL. This association was not found in the depressive phenotype, suggesting that neurodegeneration might have a minor role in patients with depressive FM. Interestingly, previous OCT studies suggested neurodegeneration is not present in patients with major depression syndrome (36), whereas neurodegeneration has been observed in the retina of patients suffering other diseases associated with depression, such as bipolar disorder (14,37). Our results on FM subtypes have not been priory reported, we believe this study might give clinicians new clues to better understand the pathophysiology of the different FM phenotypes.

No specific and conclusive tests on which to establish FM diagnosis, possible treatment alternatives or to comprehend the pathophysiology of this process exist nowadays. Thus, the search for key biomarkers is essential in these patients. Autotaxin, brain derived neurotrophic factor and other pro-inflammatory factors (such as TNF-α, IL-6, IL-10) have been found in the cerebrospinal fluid and plasma and/or serum of FM patients (38-40) and in addition there are published studies which use these markers to monitor different therapies (4). Our results might provide new options not only to facilitate the diagnosis of FM, but also to monitor these patients by using GCL results and visual function parameters as a possible biomarker for disease evolution, to follow the different disease subtypes, and be of additional support for new pathophysiology research.

This study has some limitations. First, as the sample was too small in our opinion, no logistic regression analysis in phenotypes groups was performed. Maybe due to the sample size too, our previous cross-sectional study discovered that ophthalmologic parameters did not predict disease severity in FM patients. Nevertheless, in the present study, a significant correlation between disease severity scores and alterations in GCL thickness was observed, implying that OCT changes might serve as a potential biomarker for disease progression, although prognosis is not feasible through this imaging device yet.

Second, despite changes were observed after a 5-year time lapse in the retina of FM patients as calculated by paired data analysis, no significant differences were observed between quantitative change in patients and controls over the same period. We believe this might be due the small size of the control sample, and that significant differences between both groups might be detectable if the number of controls could be increased. Last, apart from our own study, we could not find any previous published studies on retinal or visual function changes and FM syndrome, so the results of this study cannot be supported by earlier findings of external investigators. The reason is uncertain for us, although one might be the lack of positive results. This would be highly counter-productive for this type of research, as all results require to be supported (or contradict) by new findings, not only for our group, also for science in general.

In conclusion, FM causes progressive visual function loss and retinal neurodegeneration observable by SD-OCT. Progressive retinal thinning is related to an increase in disease severity, and this relationship is even stronger in the atypical and biologic FM phenotypes. This is the first longitudinal study on progressive visual and structural changes in FM syndrome. We think more studies with a larger sample size would be essential, particularly in the evaluation of treatment efficacy and the study of the pathophysiology of the disease.

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