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Fibromyalgia in Lupus Erythematosus

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Fibromyalgia has been reported to occur with high prevalence in systemic lupus erythematosus. Data on fibromyalgia in other subsets of lupus erythematosus are not available. Risk factors for fibromyalgia have not been defined. We investigated 60 patients with different subsets of lupus erythematosus for the presence of fibromyalgia, association with clinical and laboratory parameters and disease activity. Our data were compared with the multicentre lupus erythematosus registry at the Free University of Berlin. Ten out of 60 patients with more than 11 tender points and widespread pain for more than 3 months were classified as positive for fibromyalgia. All of them were female. Fibromyalgia-positive patients suffered significantly more often from headache, morning stiffness, diffuse alopecia, muscle pain, arthralgia, renal involvement, and disclosed peripheral blood cell cytopenia, rheumatoid factor, hypergammaglobulinaemia and intake of corticosteroids and azathioprine. Fibromyalgia was more frequent in systemic lupus than in other lupus subsets. Evaluation of fibromyalgia symptoms and lupus disease activity was performed in 30 patients in a 1-year (range 9–13 months) follow-up. These 30 patients consisted of 9 fibromyalgia-positive and 21 fibromyalgia-negative patients. Both groups were characterized by stable clinical features such as number of tender points and ECLAM index. Fibromyalgia did not show a correlation with lupus activity. We suggest that fibromyalgia and lupus erythematosus are distinct complaints. Patients with lupus are at risk of developing secondary fibromyalgia. The clinical features of fibromyalgia-positive patients may contribute to misinterpretation of lupus activity. *Key words: fibromyalgia; lupus erythematosus.*

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Fibromyalgia (FM) is a syndrome of widespread pain, decreased pain threshold, sleep disturbance, fatigue, and distress. The aetiology is not completely understood but there is increasing evidence for a central nervous neuroendocrine and immune dysfunction (1–4).

Whilst 1–3% of the general population is affected, the prevalence of FM in people with systemic lupus erythematosus (SLE) has been reported to be as high as 22–61% (5–8). This type of FM associated with an "underlying disorder" has also been defined as secondary FM. Prognostic factors for the development of FM in lupus patients have not been established.

Previous studies have shown that secondary FM has an impact on quality of life, working ability and efficacy. Furthermore, FM can lead to misinterpretation of lupus disease activity and therefore to overtreatment (6).

In this study we analysed the prevalence of FM in a group of 60 patients with different subsets of lupus, including SLE, with the aims of determining whether secondary FM is also associated with limited forms of lupus disease, and to define clinical characteristics for lupus erythematosus (LE) patients with secondary FM.

MATERIALS AND METHODS

Patients

A total of 60 out-patients with definitive LE but without myopathy, myositis, osteoporosis or thyroidal disorders were included in this study. All the patients had been examined by a dermatologist, a rheumatologist and a specialist in physical medicine in our interdisciplinary connective tissue clinic (9). SLE was classified as suggested by the American Rheumatologists Association (ARA; 10). Chronic discoid LE was diagnosed upon typical clinical lesions with follicular hyperkeratosis (plugging) and scarring, histology and direct immunofluorescence ("lupus band"). Subacute LE was defined as LE with either follicular erythematous papules or annular erythematous plaques, photosensitivity, antibodies against Ro/La, histology and "lupus band" test. The selection criteria for this study were (i) reference to our outpatient clinic, (ii) proved LE and (iii) patient consent.

FM was classified according to the American College of Rheumatology (ACR) criteria (11). Lupus activity was scored according to the index suggested by the Consensus Study Group of the European Workshop for Rheumatology (ECLAM index; 12, 13).

Medical history and clinical examination

All patients were asked about symptoms characteristic for FM (4, 11). The medical records were reviewed for general parameters: age, age at diagnosis of LE, duration of lupus disease, ARA-criteria for SLE. Moreover, the cumulative doses of major medications like prednisolone equivalent, azathioprine, chloroquine and hydroxychloroquine were estimated.

Thereafter, a complete standardized clinical examination of the musculoskeletal system, a neurological examination and finger palpation of the 18 tender points with a force of approximately 4 kg/cm^2 were performed. Functional spine parameters were obtained. Palpation of painful muscles was performed to disclose any muscular hypertonus.

In 30 patients a second examination was performed 1 year (9–13 months) later. Our data were compared with the data pool of the multicentre LE registry (14).

Laboratory parameters

Antinuclear antibodies were determined by indirect immunofluorescence on HEp2-cells. DsDNA-antibodies, antibodies to extractable nuclear antigens (ENA) and cardiolipin-antibodies were determined by ELISA. Results greater than 40 U/ml for dsDNA-antibodies, greater than 25 U/ml for ENA, greater than 6 U/ml for cardiolipin-IgM and greater than 10 U/ml for cardiolipin-IgG were considered positive.

Furthermore, routine laboratory tests were performed. Leukocyte counts less than 4000/mlat two evaluations were considered as leuko-

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Table I. *Comparison of clinical and laboratory findings in FM-positive and FM-negative patients with lupus erythematosus*

Parameter	FM-positive (Jena) A	FM-negative (Jena) B	LE-registry (Berlin) C	Significance	
				A vs. B	A vs. C
LE subsets					
SLE	8/10	21/50	53/338	$p<0.03$	$p<0.005$
Other subsets	2/10	29/50	285/338	n.s.	n.d.
Fatigue	10/10	32/50	145/338	$p<0.01$	$p<0.00026$
Morning stiffness	10/10	16/50	60/338	$p<0.0007$	$p<0.000005$
Muscle tenderness	10/10	22/50	n.d.	$p<0.0008$	n.d.
Enthesopathy	10/10	14/50	n.d.	$p<0.0003$	n.d
Lumbalgia	10/10	22/50	n.d.	$p<0.0008$	n.d.
Cervicalgia	10/10	21/50	n.d.	$p<0.0006$	n.d.
Muscle pain	10/10	21/50	84/338	$p<0.0006$	$p<0.000005$
Psychic symptoms	8/10	19/50	n.d.	$p<0.01$	n.d.
Oral ulcers	3/10	0/50	20/337	n.s.	$p<0.03$
Sicca syndrome	6/10	6/50	n.d.	$p<0.002$	n.d.
Renal involvement	7/10	5/50	47/328	$p<0.02$	$p<0.0086$
Irritable bowel	4/10	4/50	n.d.	$p<0.02$	n.d.
Swelling of the hands	9/10	24/50	n.d.	$p<0.01$	n.d.
Diffuse alopecia	9/10	10/50	58/338	$p<0.000005$	$p<0.000005$
Cardiolipin-IgM-antibodies	5/9	9/45	47/103	$p<0.04$	$p<0.04$
Cardiolipin-IgG-antibodies	7/9	17/45	46/108	$p<0.03$	n.s.
Hypogammaglobulinaemia	4/10	5/50	n.d.	$p<0.03$	n.d.
Hypergammaglobulinaemia	6/10	20/50	48/318	n.s.	$p<0.0019$
Rheumatoid factor	5/7	18/32	27/316	n.s.	$p<0.00013$
Leukopenia	6/10	14/50	44/333	n.s.	$p<0.0019$
Lymphopenia	9/10	32/50	115/332	n.s.	$p<0.0006$
Thrombopenia	5/10	18/50	25/326	n.s.	$p<0.0007$

n.d. not done; n.s. not significant.

penia, lymphocyte counts less than 20% at two evaluations as lymphopenia and thrombocyte counts less than 100,000/ml as thrombopenia.

Comparison with the LE registry

The lupus registry at the Department of Dermatology of the Free University of Berlin was established to obtain a multicentre data pool on lupus disease (14). FM was not included as a special item, but for each of the following parameters comparison was made: muscular pain, arthralgias, arthritides, morning stiffness, fatigue, major medications (corticosteroids/azathioprine/chloroquine/hydroxychloroquine), headache/migraine, CNS involvement, renal involvement, cytopenia, photosensitivity, Raynaud's syndrome, oral ulcers, "lupus band" test, autoantibodies (dsDNA, ANA, Ro, La, Sm, Scl70, U1RNP, cardiolipin-IgG and -IgM), rheumatoid factors, diffuse alopecia, thrombosis, acrocyanosis, low serum complement, increased liver enzymes, hypergammaglobulinaemia, LE subsets.

Statistical analysis

For statistical analysis of the clinical and laboratory parameters chi-square-test for crosstabs was used. Age at lupus manifestation, disease duration of lupus erythematosus, ECLAM index and number of ARA criteria fulfilled were compared by Whitney-Mann-U test. Results with $p<0.05$ were considered significant.

RESULTS

Results of the first series of examinations

Ten out of 60 patients with more than 11 tender points and widespread pain for more than 3 months were classified as positive for FM. Eight patients had SLE ($p<0.03$). Only two patients with other types of lupus suffered from FM (1 with CDLE, 1 with lupus profundus). The occurrence of FM in non-SLE subsets was not significant.

Gender, age and age at disease onset. All patients with secondary FM and 37 of the non-FM patients were female ($p>0.05$). The mean age of patients in the FM group was 52.9 years (range 37–69 years) compared with 48.1 years (range 24–73 years) in the non-FM group. The average age at the diagnosis of LE was 39.9 years (range 23–55 years) in the FM group vs. 35.0 (range 12–64 years) in the non-FM group. These differences were non-significant.

Disease duration of LE was determined from the time of diagnosis to be 152.7 months (range 22–401 months) in the FM group and 159.7 months (range 13–526 months) in the non-FM group ($p>0.05$).

Therapy. The average cumulative dosages of medications were approximated from a retrospective analysis. Statistical analysis was not performed, but these rough calculations suggest, that FM-positive patients obtained higher cumulative dosages of corticosteroids and azathioprine as FM-negative (415 mg vs. 295 mg, range 37–1319 mg and 0–6024 mg, respectively).

General and laboratory parameters (Table I). Not surprisingly general fatigue, morning stiffness, muscle tenderness and pain, enthesopathy, lumbalgia, headache and paresthesia, irritable bowel, swelling of the hands and psychological disturbance are more common in FM-positive patients with SLE than in FM-negative patients. Also diffuse alopecia, Sicca syndrome and renal involvement are more frequent in the FM-positive group of patients. Laboratory investigations disclosed a higher frequency of cardiolipin antibodies (IgG and IgM

type) and hypogammaglobulinaemia. Other parameters, in particular immunological ones, showed no statistically significant difference between both groups of patients. In comparing our data with the lupus erythematosus registry, clinical differences in FM-positive patients within the whole group of LE patients have been shown (Table I). In addition to the differences mentioned above, a higher frequency of rheumatoid factor ($p < 0.00013$) and cytopenia ($p < 0.0007 - 0.0009$) was noted among FM-positive patients. Slightly more oral ulcers were seen in FM-positive patients ($p < 0.03$).

Results of the follow-up

Evaluation of FM symptoms and lupus disease activity was performed in 30 patients in a 1-year follow-up (range 9 – 13 months): Nine FM-positive and 21 FM-negative patients. Six of them were males (all FM-negative) and 24 females. One non-FM patient with CDLE developed a renal involvement during the follow-up and was then classified as having SLE.

FM patients showed diffuse widespread pain and more than 11 painful tender points also at follow-up visit. The average number of positive tender points was 15 (first examination) and 16 (follow-up) in the FM group. In the non-FM group nobody developed FM. The average number of positive tender points was 2 and 1, respectively.

The ECLAM-index showed only slight differences between the two groups. At the first visit the average score was 3 (range 1 – 8) in the FM and 1.8 (range 0 – 5) in the non-FM group, and at the follow up-visit it was 2.1 (range 1 – 5) in the FM and 2.25 (range 0 – 9) in the non-FM group ($p < 0.05$).

DISCUSSION

The prevalence of FM was 16.7%, which is comparable with previous studies in SLE patients with a prevalence of 22 – 25% (4 – 7). Other LE subsets do not show an increased prevalence. It is evident that SLE patients show a much higher prevalence of FM than the general population, but is there a causal relationship?

As we know from other conditions, a relationship between reduced physical activity and FM is obvious (14). An underdeveloped dorsal musculature may lead to vertebral dysregulation due to a change in the static balance, which can induce or aggravate the symptomatic by sensomotoric reflex mechanisms (15). This point of view is supported by the significantly higher frequency of cervicalgias and lumbalgias in FM patients.

Patients with secondary FM had taken corticosteroids and immunosuppressive drugs in much higher cumulative doses. The question raised by this is whether the muscle and soft tissue pain can be attributed to a steroid myopathy. All lupus patients classified as FM-positive in this study reported generalized pain of soft tissue and muscles but none showed a muscle weakness during examination or reported such an event. In contrast to steroid myopathy, we observed a muscular hypertonus instead of muscular weakness. This observation argues against steroid myopathy as a major cause for muscle pain in FM-positive patients.

The overlapping symptoms of LE and FM can lead to misinterpretations of LE-activity (6), leading to the prescription of higher dosages of corticosteroids and immunosuppressive drugs in the FM patients. Indeed we found no significant differences in the disease activity and the number of fulfilled ARA-criteria vs. non-FM patients, but higher cumulative dosages of prednisolone and azathioprine and a more frequent intake of analgetics.

Secondary FM is a stable feature in LE patients as demonstrated by a one-year follow-up. Since no relationship to the LE activity could be confirmed in this or another study (6), the conclusion that this is the coexistence of two independent complaints is reasonable. Secondary FM brings a risk of overtreatment and misinterpretation of symptoms in SLE patients, which is of great importance when we recognize that about 50% of mortality is due to complications of therapy (7).

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