Clues to Pathogenesis of Fibromyalgia in Patients with Sickle Cell Disease

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ABSTRACT. ***Objective.*** To investigate the association between sickle cell disease (SCD) and fibromyalgia (FM).
Methods. Nine patients with SCD for whom a rheumatology consult was requested were assessed for FM by retrospective chart review. Eleven inpatients with other forms of anemia referred for rheumatology consult were also assessed for FM.
Results. Eight of 9 patients with SCD fulfilled classification criteria for FM compared to one of 11 patients without SCD ($p < 0.001$).
Conclusion. Awareness of the high frequency of FM in SCD can improve treatment of sickle cell crisis. Some pain that is labeled as sickle cell crisis pain may be due to FM, and may improve with tender point injections. (J Rheumatol 2004;31:598–600)

Key Indexing Terms:
FIBROMYALGIA SICKLE CELL DISEASE

Fibromyalgia (FM) is a chronic pain syndrome. A patient is classified with FM if he or she has widespread pain for at least 3 months in combination with tenderness in at least 11 of 18 specific tender point sites[1]. The prevalence of FM worldwide is 0.5–12%. The aim of this study was to evaluate the presence of FM in patients with sickle cell diseae (SCD).

MATERIALS AND METHODS

A retrospective chart review was performed to assess the presence of FM in patients hospitalized at University Hospital in Newark, NJ, during 2000–2001, who were seen by the Rheumatology Service secondary to SCD pain or other conditions in which the patients had anemia other than SCD.

A dolorimeter (Pain Diagnostics and Thermography, Great Neck, NY, USA) that distributes pressure evenly (approximate force 4 kg) over a discrete point was used to more objectively collect data.

Patients who agreed to have tender point injections as part of their treatment for FM received 1 cc of methylprednisolone (Depo-Medrol) 40 mg and 1 cc of lidocaine 1%.

RESULTS

Thirteen patients with sickle cell crisis were referred to the Rheumatology Section. Complete charts were available for 9 SCD patients. All were African American. All complained of fatigue and generalized aches. Two had symptoms of irritable bowel, 3 had headaches, and one had numbness and tingling in her hands. Physical examination indicated that 8 of the 9 patients (89%) fulfilled classification criteria for FM. No patient had synovitis. All 8 patients with FM had sleep disturbances. No sleep disturbance was observed in the patient with SCD who did not have FM.

Six patients were women (75%) and 2 were men (25%). The mean age (± standard error) was 28.5 years (± 3.04) (range 20–47). Range of hemoglobin was 6.1 to 9.8 mg/dl (mean ± SE 7.66 ± 0.42 mg/dl). All patients had normal thyroid-stimulating hormone and liver functions. All had negative antinuclear antibodies, human immunodeficiency virus (HIV), rapid plasma reagin, and hepatitis B tests. Two patients were positive for hepatitis C. Demographic, clinical, and laboratory features of patients with SCD with FM are summarized in Table 1.

The control group consisted of the first 11 inpatient rheumatology consultations during this period. The mean age (± SE) was 32.9 (± 2.45). Range of hemoglobin was 4.7 to 10.6 mg/dl (mean ± SE 8.49 ± 0.55). Only one of the 11 anemic patients had FM. Demographic, clinical, and laboratory features of the control group are summarized in Table 2.

Four patients with SCD received 3 or more tender point injections with methylprednisolone and lidocaine 1%. In all 4 patients the injections resulted in improvement in pain. Sickle cell crisis pain resolved following injections in one patient.

The difference in the proportion of patients with FM with SCD versus anemia due to other causes was highly significant ($p < 0.001$ using chi-squared analysis).

DISCUSSION

FM is common in patients with SCD and this is a new clinical observation. In addition, FM was found among relatively young patients with SCD (mean age 28.5 yrs). The peak age of FM is 40–60 years[2]. FM in patients with SCD was seen mostly in women, as is the case in the general

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Table 1. Demographics and clinical features of patients with SCD and FM.

Patient	1	2	3	4	5	6	7	8	9
Age, yrs	21	22	20	23	47	35	31	29	19
Sex	M	F	F	F	F	M	F	F	M
Race	AA	AA	AA	AA	AA	AA	AA	AA	AA
Type of SCD	SS	SC	SS	SS	SS	SS	SS	SS	SS
FMS	+	+	+	+	+	+	+	+	–
Pain increased with activity	+	–	–	+	+	+	+	+	–
IBS	+	–	+	+	–	–	+	–	+
Fatigue	+	+	+	+	+	+	+	+	+
Sleep disturbance	+	+	+	+	+	+	+	+	–
Headaches	–	+	–	+	–	+	–	–	–
Numbness	–	–	–	–	+	–	–	–	–
Hemoglobin	9.8	7.9	9.2	6.1	6.5	7	7.6	7.2	8.3
Creatinine	0.6	0.7	0.4	0.6	4.8	0.8	0.6	0.4	2
Hepatitis C	–	+	–	–	–	+	–	–	–

AA: African American.

Table 2. Demographics and clinical features of patients with anemia.

Patient	1	2	3	4	5	6	7	8	9	10	11
Diagnosis	4	2	1	5	6	1	3	1	4	1	1
Age	41	42	36	24	28	26	21	37	41	30	44
Sex	F	M	F	F	F	F	F	F	F	F	F
Race*	AA	AA	AA	W	AA	AA	AA	H	H	AA	AA
FMS	–	–	–	–	–	–	–	–	+	–	–
Pain increased with activity	–	–	–	–	–	–	–	–	+	–	–
IBS	–	–	–	–	–	–	–	–	–	–	–
Fatigue	+	–	+	+	+	+	–	–	+	–	–
Sleep disturbance	–	–	–	–	–	–	–	–	+	–	–
Headaches	+	–	–	+	–	–	–	+	–	–	–
Numbness	–	–	–	–	–	–	–	–	–	–	–
Hemoglobin	7.3	10.3	7.6	4.7	9.6	10.6	10.5	7.7	6.4	8.4	8.2
Creatinine	2.1	0.7	1.1	0.6	0.5	0.8	0.5	2.4	1.3	1.5	0.7
Hepatitis C	–	–	–	–	–	–	–	–	–	–	–

Diagnoses: 1: systemic lupus erythematosus; 2: rheumatoid arthritis; 3: juvenile rheumatoid arthritis; 4: Sjögren's disease; 5: Wegener's granulomatosis; 6: Crohn's disease with a spondyloarthropathy. * AA: African American; W: Caucasian; H: Hispanic.

population, in which over 80% of those with FM are women.

The etiology of FM is unclear. Conditions reported to be associated with FM include rheumatoid arthritis, Sjögren's syndrome, hypothyroidism, HIV infection, and Lyme disease. The common denominator is thought to be that peripheral pain generators may set up the central sensitization that is characteristic of FM in someone who is genetically vulnerable[3]. Peripheral pain generators are local musculoskeletal, neurological sources of local pain that contribute to the symptom burden of FM.

In SCD, oxygen saturation is lower during sleep than during wakefulness[4]. The high frequency of FM in patients with SCD may stem from sleep disturbances and nocturnal hypoxemia, which is associated with subsequent central nervous system events[4,5]. The hypoxemia in SCD can be attributed to a fall in tidal respiratory volumes and to secondary chronic pulmonary dysfunction, commonly seen in SCD[6].

Although anemia may be a contributing factor to the development of FM in SCD, it does not seem by itself to elicit this syndrome. FM was detected in only one of 11 patients with anemia not caused by SCD. SCD patients have widespread vasoocclusion that may impair blood flow and lead to metabolic changes in the muscles; this is not seen in other patients with FM[7]. Observations of increased adherence of sickled erythrocytes[8], neutrophils[9], and platelets[10] to vascular endothelial cells and endothelial cell activation[11] suggest that the vasoocclusion is more complex than just a mechanical obstruction due to sickled cells. Nocturnal

hypoxemia in SCD correlates with increased CD11b expression on monocytes and neutrophils and with platelet-erythrocyte complex formation[12], suggesting an association between oxygen saturation, inflammatory cell activation, and adhesiveness in SCD.

An inflammatory component is suggested in some patients with FM: levels of interleukin (IL)-1Ra, and IL-8 were significantly higher in FM sera than in controls[13]; IL-1ß, IL-6, and tumor necrosis factor-α were detected in the skin of 30% of FM patients, but in none of the healthy controls[14].

Awareness of the high frequency of FM in SCD can improve the treatment of pain during sickle cell crisis. Some of the pain that is labeled as sickle cell crisis pain is due to FM and improves with tender point injections. Tender point injections are part of the treatment of FM. There are few well-controlled studies[15]. A variety of substances have been found to be effective. The nature of the injected substance is not a critical factor[15]. In this study, methylprednisolone was used in the tender point injections, since there was question of chronic inflammation contributing to sickling and possibly to FM in the SCD patients.

Large prospective randomized controlled trials of patients with stable chronic SCD as well as SCD patients in crisis are needed to further evaluate whether FM is more prevalent in SCD compared to age, race, and sex matched patients with anemia. Insight into the pathogenesis of FM may be gained by better understanding the causes of FM in SCD.

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