Clinical and laboratory studies in patients with leprosy and enthesitis

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Abstract

In a combined clinical, radiological, and laboratory study of 77 patients throughout the leprosy spectrum, 10 patients had an enthesitis which has not been described previously as far as is known and which was not associated with the characteristics of erythema nodosum leprosum reactions. C reactive protein and α_1 acid glycoprotein values were significantly lowered only in those patients with leprosy and enthesitis. No radiological abnormalities were found.

Charcot joints and the arthritis associated with erythema nodosum leprosum reactions are well recognised features of leprosy.^{1,2} Rarely has an arthritis mainly affecting the joints of the wrists, elbows, knees³ and proximal joints^{4,5} been recorded. We have previously described a chronic peripheral polyarthritis in the absence of erythema nodosum leprosum reactions, throughout the leprosy spectrum,^{6,7} which was erosive in some patients.⁷ As far as we know, no studies have focused on the enthesitis, the site of attachment to bone of tendon, ligament, or joint capsule.

In a study concentrating on the synovial joints of patients with active leprosy infection⁷ patients were examined clinically and radiologically for an enthesopathy.

Patients and methods

Seventy seven patients (49 men, 28 women) with a mean age of 35.6 (SEM 14.9) years and a mean duration of leprosy infection of 9.6 (SEM 7.6) years were studied (table 1). The sex ratio was 1.7 to 1. All patients were seen in the Abou Zabel leprosy colony in Egypt. In every patient the diagnosis was based on clinical and histopathological features.⁸

Enthesitis was defined as tenderness to palpation at the site of attachment of bone to tendon, ligament, or joint capsule. At the beginning of the assessment a standard palpation over the anterior-superior aspects of the middle third of the clavicle (bilaterally) was used so that patients could compare and discriminate between pressure alone and tenderness over the entheses.⁹ Firm palpation over the sites of the entheses was used and scored either individually or as a group, the highest scoring site being recorded for the group as a whole. Sites grouped in this way were: the nuchal crests, the costochondral joints, the sacroiliac joints, and the cervical and lumbar spinous processes. The remaining sites were scored individually on both sides.⁹ Sites

were scored as follows: 0=no pain; 1=mild tenderness; 2=moderate tenderness; 3=wince or withdraw enthesitis.

The following sites of entheses were examined: the nuchal crests, the manubriosternal joint, the costochondral joints, the greater tuberosity and the medial and lateral epicondyles of the humerus, the iliac crests and the anterior iliac spines, the greater trochanter of the femur, the tibial tuberosities, the adductor tubercles, the medial and lateral condyles of the femur and tibia, the head of the fibula, the calcaneal insertions of the plantar fascia and the Achilles tendons, and the anterior posterior iliac spines. The enthesitis index⁹ and the Ritchie articular index¹⁰ were recorded for all patients.

Patients with Charcot's arthropathy and those whose limbs were abnormal on clinical neurological examination were excluded from this study. A history or physical signs suggesting seronegative spondylarthritides or recent systemic disturbance, especially gastrointestinal symptoms, also precluded entry into this study. Hepatitis B infection was excluded serologically.

RADIOLOGY

Standard views were taken of the hands, feet, knees, and spine. Radiographs were assessed by one radiologist (JPO) in the absence of the clinical and laboratory results. Only those patients with musculoskeletal symptoms were radiographed.

LABORATORY TESTS

Serum was separated and aliquots were transported on dry ice to the United Kingdom. α_1 Acid glycoprotein,¹¹ α_2 macroglobulin,¹¹ C reactive protein,¹² and IgM rheumatoid factor¹³ were determined by established methods.

Non-parametric tests (Mann-Whitney U) were used to compare data between the clinical groups.¹⁴

Results

CLINICAL FEATURES

Ten patients had a generalised enthesitis (enthesitis index range 10 to 70) (table 1).

Thirty three patients had uncomplicated leprosy, 20 patients had leprosy and the manifestations of an arthritis, and 14 patients had an erythema nodosum leprosum reaction as a complication of leprosy (table 1). The results for these patients are reported elsewhere.⁷

The history was that of an insidious development of pain and stiffness at the site of the

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Table 1 Data for all patients studied and those with enthesitis. Data are given as mean (SEM)

Leprosy type*	Number of patients	Sex (M:F)	Age (years)	Duration of disease (years)
LL	37	22:15	36.3 (14.7)	10.9 (2.5)
with enthesitis	8	3:5	39.7 (5.8)	1.6 (4.1)
BL	9	7:2	33.4 (13.4)	7.0 (1.4)
BB	7	5:2	39.3 (16.8)	4.5 (2.0)
BT	5	3:2	33.5 (7.7)	6.0 (3.1)
with enthesitis	1	F	26	4
TL	4	2:2	41.3 (4.2)	25.0 (5.0)
ENL	14	9:5	28.2 (4.2)	9.4 (3.8)
with enthesitis	1	M	55	40
IDL	1	M	5	0.5

*LL=lepromatous leprosy; BL=borderline lepromatous; BB=borderline; BT=borderline tuberculoid, TL=tuberculoid leprosy; ENL=erythema nodosum leprosum; IDL=indeterminate leprosy.

enthesitis, presenting months or years after the onset of the first symptoms of leprosy. Pain at the site of the enthesitis seemed to have no temporal correlation with type 1 or type 2 lepra reactions, nor were there any coincident features of either of these reactions. The pattern was one of chronic exacerbations and remissions, with no specific evolution, symmetry, or pattern of disease of any single enthesitis or groups of entheses either centrally or peripherally. The only consistent feature was that the number of entheses affected at any one time was never less than five. Morning stiffness lasted variably for between 15 minutes and one hour and inactivity stiffness ('gelling') varied between 10 and 15 minutes.

Synovial proliferation was not detected, nor was there clinical evidence for an underlying vasculitis. Subcutaneous or tendinous nodules, and other extra-articular manifestations of the seronegative spondylarthritides¹⁵ or rheumatoid arthritis were not detected. The symptoms and signs of the enthesopathy in the patient with the supervening erythema nodosum leprosum reaction remained unchanged during and after the reaction.

No patient with arthritis had concurrent enthesitis and no patient with an enthesitis had arthritis at that time or previously.

No radiological abnormalities were found around any of the affected entheses nor in the three available sacroiliac joint radiographs in this patient group.

LABORATORY RESULTS

Table 2 summarises the results of the Rose-Waaler test to detect the presence of IgM rheumatoid factor.

The acute phase protein values of those patients with leprosy with and without arthritis are reported elsewhere,⁷ but for clarity the values for the patients with leprosy without

musculoskeletal symptoms are given below. The values for the acute phase proteins were similar throughout the leprosy spectrum in those patients without musculoskeletal manifestations. Patients with leprosy and enthesitis were compared with those patients with leprosy alone.

C reactive protein (mean 4.2 (SEM 2.4) mg/l, $p < 0.05$) and α_1 acid glycoprotein concentrations (712 (77) mg/l, $p < 0.01$) were reduced significantly compared with patients with leprosy alone (CRP 15 (4.5) mg/l; α_1 acid glycoprotein 823 (65) mg/l). α_2 Macroglobulin concentrations (2667 (145) mg/l, $p < 0.340$) did not differ significantly from those of patients with leprosy without an enthesitis (2788 (170) mg/l).

Discussion

As far as we know, the enthesopathy described in this study has not been reported before in patients with leprosy. A few studies have focused on the musculoskeletal aspects of leprosy¹⁻⁷ but none on the systematic examination of the entheses. This may be because there has been no validated protocol reported until recently.⁹ The enthesitis described here was not localised to any specific site in any specific pattern, nor was it associated with past or present symptoms of an arthritis. This suggests that different mechanisms may be responsible for the musculoskeletal manifestations in leprosy, rather than there being a spectrum of symptoms and signs.

The most common cause for an isolated lesion at the enthesitis is trauma. Inflammatory disease at several entheses raises the possibility that one of the seronegative spondylarthritides might have been responsible, but absence of evidence in the past history, family history, clinical presentation, and examination, supported by normal sacroiliac joint radiographs in three patients, make this unlikely. The overt manifestations of the seronegative spondylarthritides may not present for many years, however, making it difficult to refute this suggestion entirely.

The incidence of IgM rheumatoid factor is often high in Third World countries and in patients with leprosy.^{16, 17} In this study two of 10 (20%) patients with leprosy and enthesitis had a positive IgM rheumatoid factor in their serum compared with 22 of 33 (66%) patients with leprosy without any musculoskeletal problems. The number of patients with an enthesitis is too small, however, to determine whether there is an association with IgM rheumatoid factor. Although rheumatoid arthritis cannot be excluded, no patient with an enthesitis was suffering from an arthritis or clinically apparent vasculitis. The large number of patients, the predominance of men, and the lack of extra-articular manifestations of rheumatoid arthritis also make this possibility unlikely.

All but one patient had lepromatous leprosy. Possibly, this enthesitis is a manifestation of chronic erythema nodosum leprosum. The lack of a temporal correlation with erythema nodosum leprosum and the absence of clinical signs of that lepra reaction suggest that this is not the case.

Table 2 Rose-Waaler results found in patients with leprosy alone and in patients with leprosy with arthritis or enthesitis or erythema nodosum leprosum (ENL) reactions

Time	ENL (n=14)	Arthritis (n=20)	Enthesitis (n=10)	Leprosy (n=33)
1/32	2	4	1	5
1/64	1	1	0	7
1/128	1	3	1	9
1/1024	0	0	0	1
Total positive	4	8	2	22

α_2 Macroglobulin and α_1 acid glycoprotein bind and transport potentially destructive enzymes released at the site of tissue destruction.¹⁸ C reactive protein concentration rises in response to any chronic inflammatory disease affecting the synovial joint¹⁹ and may rise particularly steeply in response to tissue damage by bacteria rather than by other agents. A significant fall in α_1 acid glycoprotein concentrations has been noted in other causes of an infective enthesitis, suggesting its increased consumption.²⁰ In this case, however, an increase in C reactive protein would be expected, as seen in patients with leprosy and arthritis,^{2 6 7} rather than a decrease as we report here. An alternative explanation is reduced synthesis of both reactants.

Owing to the isolated environment of the leprosy colony no details of the incidence or prevalence of an enthesitis in patients with leprosy is available. This study highlights the possibility that an enthesitis may be a facet of leprosy infection and that significantly low concentrations of α_1 acid glycoprotein and C reactive protein may mark the enthesitis in patients with leprosy.

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- 1 Karat A B A, Karat S, Job C K. Acute exudative arthritis in leprosy: rheumatoid-like syndrome in association with erythema nodosum leprosum. *Br Med J* 1966; **iii**: 770-3.
- 2 Ramu G, Balakrishnan S. Arthritis in lepromatous leprosy: clinical features and biochemical findings. *Leprosy in India* 1968; No 2: 1-8.
- 3 Alcocer J V, Herrera C L, Gudino J, Fraga A. Inflammatory

- arthropathy in leprosy [Abstract]. *Arthritis Rheum* 1979; **22**: 597.
- 4 Lele R D, Sainani G S, Sharma K D. Leprosy presenting as rheumatoid arthritis. *J Assoc Physicians India* 1965; **13**: 275-7.
- 5 Modi T H, Lele R D. Acute joint manifestations in leprosy. *J Assoc Physicians India* 1969; **17**: 247-54.
- 6 Atkin S L, Welbury R R, Stanfield E, Beavis D, Iwais B, Dick W C. Clinical and laboratory studies of inflammatory polyarthritis in patients with leprosy in Papua New Guinea. *Ann Rheum Dis* 1987; **46**: 688-90.
- 7 Atkin S L, El-Ghobarey A, Kamel M, Owen J P, Dick W C. Clinical and laboratory studies of arthritis in leprosy. *Br Med J* 1989; **298**: 1423-5.
- 8 Ridley D S, Jopling W H. Classification of leprosy according to immunity: a five group system. *International Journal of Leprosy* 1966; **34**: 255-73.
- 9 Mander M, Simpson J M, McLellan A, Walker D, Goodacre J A, Dick W C. Studies with an enthesitis index as a method of clinical assessment in ankylosing spondylitis. *Ann Rheum Dis* 1987; **46**: 197-202.
- 10 Ritchie D M, Boyle J A, McInnes J M, et al. Clinical studies with an articular index for the assessment of joint tenderness in patients with rheumatoid arthritis. *Q J Med* 1968; **37**: 393-406.
- 11 Deaton C D, Maxwell K W, Smith R S, Crevelling R L. Use of laser nephelometry in the measurement of serum proteins. *Clin Chem* 1975; **22**: 1465-9.
- 12 Rubinstein K E, Schneider R S, Ullman E F. "Homogeneous" enzyme immunoassay: a new immunochemical technique. *Biochem Biophys Res Commun* 1972; **47**: 846-51.
- 13 Waaler E. On the occurrence of a factor in human serum activating the specific agglutination of sheep red corpuscles. *Acta Pathologica et Microbiologica Scandinavica* 1940; **17**: 172-8.
- 14 Nie N H, Hull C H, Jenkins J G, Steinbrenner K, Bent D H. *SSPS; statistical package for the social sciences*. New York: McGraw-Hill, 1975.
- 15 Wright V. Relationship between ankylosing spondylitis and other spondylarthritides. In: Moll J M A ed. *Ankylosing spondylitis*. London: Churchill Livingstone, 1980: 42-52.
- 16 Cathcart E S, Williams R C, Ross S H, et al. The relationship of the latex fixation test to the clinical and serological manifestations of leprosy. *Am J Med* 1962; **56**: 545-52.
- 17 Gonzales-Pares E N, Franco A E, De La Cruz S, Molares F R, Gonzales-Alcover R, Bryan R M. False positive latex in a tropical area. *J Chronic Dis* 1973; **26**: 31-8.
- 18 Koj A. Acute phase reactants. In: Allison A C, ed. *Structure and function of plasma proteins*. London: Plenum Press, 1974: 73-125.
- 19 Carr W. Acute phase proteins. In: Jeffery M S, Dick W C, eds. *The role of the laboratory*. London: Saunders, 1983: 227-339.
- 20 Becker G J, Walberg M, Hughes G R V, Pepys M B. Value of C-reactive protein measurement in the investigation of fever in systemic lupus erythematosus. *Ann Rheum Dis* 1980 **39**: 50-2.