

Proposed Criteria for Early Detection of Leprotic Arthropathy

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Abstract

Leprosy is a chronic mycobacterium disease infectious in some cases primarily affecting the peripheral nervous system and secondarily involving skin specially the melanocyte and certain other tissues [1].

Road, [2] stated that, even countries with developed health services leprosy often diagnosed only in an advanced stages of the disease due to:

1. In most societies, leprosy is not endemic and occurs only as an imported disease of minor public health importance.
2. Little attention is being paid to teaching leprosy in medical schools moreover, chapters of leprosy in general textbooks are not always updating.
3. Traditional fear is still common, the patients are often reluctant to expose themselves as leprotic patients because the fear of restrictive measure.

From this study we could conclude recent criteria for early detection and diagnosis of leprotic arthropathy.

Introduction

Leprosy is a chronic mycobacterial disease infectious in some cases, primarily affecting the peripheral nervous system and secondarily involving skin specially the melanocyte and certain other tissues [3].

Road, [2] stated that, even in countries with developed health services leprosy often diagnosed only in advanced stages of the disease due to:

1. In most societies, leprosy is not endemic and occurs only as an imported disease of minor public health importance.
2. Little attention is being paid to teaching leprosy in medical schools. Moreover, chapters of leprosy in general textbooks are not always updated.
3. Traditional fear is still common, the patients are often reluctant to expose themselves as leprotic patients because the fear of restrictive measure.

Considerable attention has been directed to the dermal,

neural and osseous complications of leprosy [3].

Reports of joint involvement in leprosy have been published since the 1960s [4,5] but the main aspect of interest in this work was to study the joint involvement in leprosy patients not in reaction since the arthritis in Leprosy reaction type 2 is well known [6,7].

Aim of the Work

Was the early detection and diagnosis of Leprotic arthropathy among EGYPTIAN Leprotic patients & their household contacts?

Patients and Methods

Sixty leprotic patients with their ninety two household contacts suffering from musculoskeletal disorders in addition to sixty control subjects were included in the study. All patients and their household contacts were selected from Abou-Zaabal, Al-Safieh, Masowd villages, (Al Kalyobia Governorate.)

The patients were 42 AND 18, their ages ranged from 15-60 years with mean (44.83 ± 4.70). The household contacts were 56 and 36, their age ranged from 12-58y) with mean (32.03 ± 11.99) with no family history of leprosy with no known exposure to leprosy, they were randomly chosen from the medical and nurse staff members. The patients selected were already diagnosed with leprosy, but not classified into any type of leprosy as the classification requires pathological exam. And the conversion to any other type occurs without any rule.

All patients, their household contacts and the control group were submitted to:

Careful family history, full clinical exam, Radiological exam, Routine lab, Investigations and serum anti-Phenolic Glycolipid I (Anti-PGL) which is a unique constituent in the inner layer of the cell wall of *mycobacterium leprae* and it appear to differ from that of all other Mycobacteria [8]. The small and large joints were examined from all aspects according to:

= Spread-severity index [9].

=Ritchie index [10] was used for the assessment of joint tenderness as follow:

=Radiological examination: The scoring system for

Table 1: shows the percentage distribution of joint involvement among the studied groups according to ss. Index (1986).

		Cases		Contacts		Controls		
		No.	%	No.	%	No.	%	
TMJ	0	54	90	92	100	60	100	$p > 0.05$
	I	6	10	0	0	0	0	
Cer.spine	0	38	63.3	74	80.4	52	86.7	$P > 0.05$
	I	22	36.7	18	19.6	8	13.3	
	II	0	0	0	0	0	0	
St. Clav.	0	52	86.6	88	95.7	60	100	$p > 0.05$
	I	4	6.7	4	4.3	0	0	
	II	4	6.7	0	0	0	0	
ACJ	0	54	90	92	100	60	100	$p < 0.05$
	I	6	10	0	0	0	0	
GHJ	0	56	93.4	92	100	60	100	$P > 0.05$
	I	2	3.3	0	0	0	0	
	II	2	3.3	0	0	0	0	
Elbow	0	58	96.7	90	97.8	60	100	$p > 0.05$
	I	2	3.3	2	2.2	0	0	
Wrist	0	33	76.7	43	93.5	30	100	$p < 0.001$
	I	3	10	3	6.5	0	0	
	II	4	13.3	0	0	0	0	
MCPS	0	42	70	84	91.4	60	100	$p < 0.001$
	I	14	23.3	4	4.3	0	0	
	II	4	6.7	4	4.3	0	0	
PIPS	0	36	60	84	91.4	60	100	$p < 0.01$
	I	12	20	4	4.3	0	0	
	II	0	0	4	4.3	0	0	
	IV	12	20	0	0	0	0	
DIPS	0	22	36.7	86	93.4	60	100	$p < 0.001$
	I	18	30	4	4.4	0	0	
	II	2	3.3	2	2.2	0	0	
	IV	18	30	0	0	0	0	
Hips	0	58	96.7	92	100	60	100	$p > 0.05$
	I	2	3.3	0	0	0	0	
Knees	0	28	46.6	68	47	52	86.6	$p < 0.001$
	I	12	20	12	13	4	6.7	
	II	16	26.7	6	6.5	4	6.7	
	III	4	6.7	6	6.5	0	0	
Ankle	0	52	87.7	92	100	60	100	$p < 0.05$
	I	6	10	0	0	0	0	
	II	2	3.3	0	0	0	0	
Subtalar	0	56	93.3	92	100	60	100	$P > 0.05$
	I	4	6.7	0	0	0	0	
MTPS	0	44	73.4	88	95.7	60	100	$p < 0.001$
	I	8	13.3	4	4.3	0	0	
	II	8	13.3	0	0	0	0	

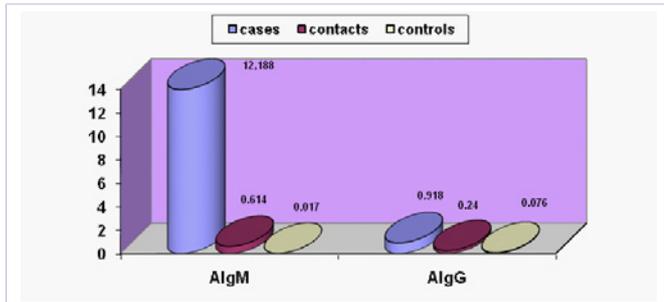


Figure 1

radiographs was done according to Larsen, et al. [11].

=Serum samples: The skin area selected was carefully sterilized.

5ml of blood were withdrawn by clean syringe and transferred to clean dry sterilized tube, which was hold in vertical position for one hour.

The tube was centrifuged for 15 minutes to separate the serum. The serum was taken to another clean dry sterilized tube capped and stored at 70°C until used.

Assessment of anti-PGL-1 antibody in the serum by using the ELISA method described by Cho, et al. [8] with minimal modifications [12]. The semi-synthetic antigen (Neoglycoprotein ND-O-BSA) was kindly provided by Dr. R.J.W. Rees, National institute for medical research, London.

It was dissolved in carbonate coating buffer (9.6pH) by sonication for 10 seconds and adjusted to final concentration of 2ug/ 1ml in the same buffer.

Results

The results of this work will be summarized in the following tables and figures:

No significant differences between cases, contacts and the control group was found for tempromandibular, glenohumeral affection and elbow joint, ($p > 0.05$) according to spread severity index. But the acromioclavicular joints were significantly more involved among cases than other groups ($p < 0.05$). The wrist, Distal Interphalangeal (DIP) and Metatarsophalangeals (MCP) and the Proximal Interphulyngenals (PIPs) were highly significantly involved in cases than in other groups ($p < 0.001$).

In the lower limb joints hips and subtalar joints were not significantly different between the studied groups ($P > 0.05$). The knees, Metatarsophalangeal (MTPs) ($p < 0.001$) and ankle joint ($p < 0.05$) were more involved among cases than in other groups (Table 1).

The mean serum level of AGLI (A IgM) antibodies was high in cases than in contacts and control ($p < 0.0001$) and in contacts than in control ($p < 0.0001$) (Table 2) because all of the household contacts and the control group had a level titration below 10, the confidence limit between this two groups was done and there was a very highly significant increase in serum APGL-I (A IgM) in contacts than in control group $p < 0.0001$ (Table 3).

The serum level of APGLI (A IgG) antibodies was also significantly higher in cases than contacts and control groups $p < 0.0001$, and in contacts than in controls with a very high significant difference $p < 0.0001$ (Tables 4,5).

As regards the skin manifestations, the hypo pigmented, hypo esthetic skin rashes were detected more among case than in contacts and control groups $p < 0.001$.

Hyper pigmentation and ulcers were significantly more frequent in cases than in the other two group's $p < 0.01$.

No significant difference between all studied groups as regards Nodules, Raynaud's and urticarial rashes (Table 6).

Discussion

Arthritis is one of leprosy manifestations which may

Table 2: Shows the serum level of APGL-1 (A IgM) antibodies in the studied groups.

	Cases		Contacts		Controls	
	No.	%	No.	%	No.	%
< 10	26	43.4	92	100	60	100
10 -	20	33.3	0	0	0	0
20 -	10	16.7	0	0	0	0
30 -	2	3.3	0	0	0	0
40	2	3.3	0	0	0	0
Total	60	100	92	100	60	100
	$X^2 = 51.29$		$p < 0.0001$			
Mean ± SD	± 12.188 ± 10.97		0.614 ± 0.434		0.017 ± 0.034	
Range	0.740 - 45.66		0.001 - 1.75		0.0 - 0.106	

Table 3: shows the serum level of APGL-1 (A IgM) antibodies in both contacts and controls.

	Contacts		Controls	
	No.	%	No.	%
< 0.01	2	2.2	48	80
0.01 -	4	4.3	12	20
0.10 -	6	6.5	0	0
0.20 -	6	6.5	0	0
0.30 -	14	15.2	0	0
0.40 -	12	13	0	0
0.50 -	18	19.6	0	0
0.60 -	2	2.2	0	0
0.80 -	2	2.2	0	0
0.90 -	10	10.9	0	0
1.0 -	6	6.5	0	0
1.1 +	10	10.9	0	0
Total	92	100	60	100
Mean ± SD	0.614 ± 0.434		0.017 ± 0.034	
	$t = 3.64$		$p < 0.0001$	

simulate rheumatoid arthritis. Hanafi, et al. [13] stated that the most commonly involved joints in leprotic arthritis were: elbow (84%), wrist (80%), MCP (80%), PIP (80%), DIP (85%), knee (66%), ankle (72%), TMJ (66%), and MTP (60%). Karat et al 1967 stated that a true arthritis may occur particularly in Erythema Nodosum Leprosum (ENL) which is a reaction state in lepromatous leprosy. The musculoskeletal manifestations may be an important cause of continuing morbidity in leprosy [14]. During the past decade, serological tests for detection of *anti-mycobacterium leprae* antibodies have been developed, among them, the Enzyme-Linked Immunosorbent Assay (ELISA) using the purified Phenolic Glycolipid-I (PGL-I) from the cell wall as a *Mycobacterium leprae* specific antigen has proved to be potentially useful for the serological study of leprosy patients, household contacts and normal individuals due to its simplicity, sensitivity as well as its capability of handling large numbers of sera simultaneously [15].

Buchanan, et al. [15] observed that elevated levels of Anti-Phenolic Glycolipid I (APGL-I) will precede the clinical diagnosis in most cases, and reported the development of leprosy in 2 out of 18 household contacts with persistent seropositivity, and found no cases among 94 household contacts who were persistently seronegative (50) or only transiently positive (44) followed for 30 months. Early diagnosis and chemotherapeutic intervention is the most essential prerequisite for decreasing deformities associated with leprosy [16].

Initiation of the antibody responses generally requires a much lower antigenic load and, therefore, should precede the clinical diagnosis. Thus antibodies, particularly IgM and IgG isotypes, should aid in the early diagnosis of infection in leprosy [17].

APGL-I (IgM) was significantly higher among cases than household contacts and control group, ($p < 0.0001$, Mean = (12.188 ± 10.97). Also among household contacts than controls ($p < 0.0002$, Mean = (0.614 ± 0.434). Our findings were consistent with those of some other studies [18,19].

APGL-I (IgG) was significantly higher among cases than household contacts and control group ($p < 0.0001$, Mean = (0.918 ± 0.714). Also among household contacts than normal controls ($p < 0.0002$, Mean = (0.240 ± 0.136) in consistent with studies that

Table 4: Shows the serum level of APGL 1 (A IgG) antibodies in the studied groups.

	Cases		Contacts		Controls	
	No.	%	No.	%	No.	%
< 1	42	70	92	100	60	100
1 -	12	20	0	0	0	0
2 -	4	6.7	0	0	0	0
3 -	2	3.3	0	0	0	0
Total	60	100	92	100	60	100
	$X^2 = 51.29$		$p < 0.0001$			
Mean ± SD	0.918 ± 0.714		0.240 ± 0.136		0.076 ± 0.052	
Range	0.420 - 3.100		0.017 - 0.498		0.009 - 0.195	

were done by Hasan, et al. and Meeker, et al. [20,21].

Erythrocyte Sedimentation Rate (ESR) was higher among 28 out of 60 leprotic patients and 38 out of 92 household contacts and only 4 out of 60 normal controls and this is consistent with the previous study that done by [13].

The serological data revealed a clear age - related correlation with the serum level of anti PGL-I (IgM) among the household contacts only. The seropositivity rate associated with high titration were found to increase rapidly up to the age of 10-19 years [i.e. in this range of age, there is a significant positive correlation with anti-PGL-1 (IgM)], followed by a steady decrease throughout the older ages [above age of 20 years, there is no significant correlation with anti-PGL-I (IgM)]. However Anti PGL-I (IgG) showed no correlation with the age. Our results agreed with the study were done by Fine, et al. [22]. Overall IgM and IgG levels have been reported to increase during youth and to decrease subsequently with increasing age [23].

Several circumstance may lead to such an age trend. Most likely a peak in the seropositivity rates in the young group reflects a high exposure to infection during this age or the foregoing period [22].

In the present study there was no detected difference in seropositivity rates among males and females, in contrast to the population - based study in Malawi that was done by Fine, et al. [22].

Correlating the mean serum level of anti-PGL-I (IgM, IgG) with ESR and latex test for Rheumatoid Factor (RF) for all the studied groups, revealed that anti-PGL-I (IgM, IgG) were significantly correlated to ESR among the household contacts only and significantly correlated to latex test for RF in both leprotic patients and household contacts. The elevation of ESR can be explained on the basis of stimulation of the immune response by the infection with *Mycobacterium leprae* resulting in hypergammaglobulinaemia [24] or it may represent Arthur phenomena [25]. So, ESR may be considered as a parameter for activity in case of acute or sub-acute leprotic infection.

In the present study, the rheumatological examination showed that the most commonly involved joints among the leprotic patients as well as household contacts were: the Distal Interphalangeal (DIP) 63.3%, Metacarpophalangeal (MCP) 30% metatarsophalangeal 26.6% followed by wrist 23.3%, ankle 13.3% and acromioclavicular joint 10%, but the arthritis was significantly higher in leprotic patients than household contacts according to the (SS index) where p value was < 0.01 , < 0.05 , < 0.05 , < 0.01 , < 0.05 , < 0.05 respectively. This is consistent with the previous study by Hanafi, et al. [13], who found the same findings with exception of the elbow joint which was involved in 3.3% corresponding to 84% in the study which was done by Hanafi, et al. [13]. Among the household contacts, the most commonly involved joint was the knee joint 26% corresponding to 53.4% among the leprotic patients ($p > 0.05$). Hanafi, et al. [13] reported that the knee joint was involved in 72% in leprotic patients.

Our study highlights, however that a symmetrical polyarthrititis

Table 5: Shows the serum level of APGL 1 (A Ig M-G) antibodies in both contacts and controls.

	Contacts		Controls	
	No.	%	No.	%
< 0.1	16	17.4	40	66.7
0.1 -	26	28.3	20	33.3
0.2 -	22	23.9	0	0
0.3 -	10	10.9	0	0
0.4 -	18	19.5	0	0
Total	92	100	60	100
Mean ± SD	0.240 ± 0.136		0.076 ± 0.052	
	t = 3.57		p < 0.0001	

Table 6: shows comparison between all of the studied groups as regards skin Manifestations.

	Cases affected		Contacts affected		Controls affected		
	No.	%	No.	%	No.	%	
Hypo pigmentation	28	46.7	4	4.3	0	0	< 0.001
Hyper pigmentation	18	30	6	6.5	0	0	< 0.01
Ulcers	10	16.7	2	2.2	0	0	< 0.01
Nodules	8	13.3	6	6.5	0	0	> 0.05
Raynaude's	10	16.7	12	13	0	0	> 0.05
Urticaria	4	6.7	8	8.7	0	0	> 0.05

of the synovial joints may be a facet of the leprosy infection.

As regards the enthesopathic lesions, it was found that the suprapinatus enthesis was significantly involved in leprotic patients than household contacts and control group. The lateral epicondyle of humerus was the most common involved enthesis. This could imply that the enthesopathy may be one of the early rheumatic manifestations of leprosy and therefore may consider as a reactive arthropathy for a well-known pathogen as reported by Inderpal and Surrinder, et al. [25].

Both anti -PGL-I (IgM) and (IgG) was significantly correlated to the enthesopathy among the household contacts only.

As regards skin manifestations, it was found that hypopigmentation and hyperpigmentation were detected more among the leprotic patients than the household contacts and control group with a very highly significant difference $p < 0.001$ and < 0.01 respectively. This may be due to the fact that melanocytes like nerves are derived from the neural crest and there is a special affinity between *Mycobacterium leprae* and all the neural crest tissues further the role of melanin in the metabolism of *Mycobacterium leprae* [26].

Radiological examination of all the studied groups showed some abnormalities in both upper and lower limbs among both leprotic patients and their household contacts as follows:

X-ray hand of leprotic patients showed soft tissue swelling

(23.3%), osteoporosis which may be localized (juxta - articular) or generalized (13.3%), periosteitis, joint space narrowing and bone absorption (10%), deformities and ankylosis (10%). This is consistent with the study done by Hanafi, et al. [13] who found the same changes, while the only changes which could be detected among the household contacts was juxta-articular osteoporosis (15.2%).

Dinarelo, [27] stated that IL-1, IL-6 and TNF are a major cytokines produced by macrophages of leprosy and these cytokines stimulate immunological inflammatory reactions. In contrast, IL-10 inhibits macrophage functions and influences the subsequent macrophage/T cell interaction [28].

TNF enhanced the production of reactive nitrogen oxide and inhibits mycobacterial growth in human macrophages.

IL-1, stimulates the liver cells to secrete the acute phase reactants [29]. TNF together with IL-1 produce juxta articular O.P [30].

Waters, [31] reported that X-ray hand of the untreated lepromatous leprosy patients may reveal asymmetrical phalangeal cysts, presumed to be due to lepromatous infiltration.

Inderpal and Surrinder, [25] stated that osteoporosis around the affected joints, at times, was more than what could be expected from disease and reported a reduction in transverse trabeculae in the subcortical layer and a diminution of longitudinal layers of trabeculae in the cortex.

Plain X-ray elbows showed Charcot's joint in two leprotic patient (3.3%) and soft tissue swelling in 10 patients (16.7%). No radiological changes could be detected among the elbows of household contacts.

Radiological examination of the knees showed soft tissue swelling in 18 leprotic patients (30%) versus 8 household contacts (8.7%), osteoporosis in 8 leprotic patients (13.3%) versus 4 household contacts (4.3%), periosteitis and joint space narrowing in 8 leprotic patients (13.3%) versus 2 household contacts (2.2%). X-ray ankle showed soft tissue swelling in 8 leprotic patients (13.3%) versus 6 household contacts (6.5%), osteoporosis in 10 leprotic patients (16.7%) versus 10 household contacts (10.9%), bone absorption and deformities in 4 leprotic patients (6.7%) only. Hanafi, et al. [13] reported that in some long standing cases whether treated or untreated, there is absorption of the terminal phalanges and typical penciling of the heads and shafts of metatarsal bones. All of these radiological changes were significantly higher in leprotic patients than household contacts and control groups ($p < 0.0001$, $p < 0.001$).

In the present study, the severity of arthritis was significantly correlated to latex test for RF among the leprotic patients only. Simulating what happens in rheumatoid arthritis, Cats and Hazevoet, [32] observed that patients with a positive test for RF in the blood have more severe clinical disease and complications than do seronegative patients. Allen, et al. [33] observed that increased levels of IgG RF have been associated with a high frequency of subcutaneous nodules, vasculitis, elevated ESR,

decreased complement levels and increased numbers of joint involvement.

Correlating ESR to the other studied variables, it was found that ESR was significantly correlated to both RF and the enthesopathy among the household contacts only.

Conclusion

Finally we can conclude that the present study showed that the radiological changes started early as a soft tissue swelling and osteoporosis with or without signs of arthritis in household contacts, and proved that the radiological changes is one of the suggestive diagnostic manifestations of musculoskeletal leprosy which should be confirmed by serological investigation (APGL-I) which was significantly correlated to the enthesopathy index.

This study gives a chance for the early detection and management of leprosy through the laboratory investigations as well as clinical and radiological examination. On the other hand, unexplained early radiological changes especially in an endemic area should be investigated for leprosy until proved otherwise, whatever, associated with arthritis or not.

Lastly we could suggest the following criteria for the early diagnosis of leprosy which might be:

1. A positive APGL-I ($IgM > 0.085$, $IgG > 0.0180$).
2. High enthesopathy index > 10
3. Skin manifestations (hypo or hyper pigmented patches)
4. Loss of hair especially eye brows
5. Arthralgia and / or arthritis in attacks: RA like, or monoarticular
6. Peripheral nerve thickening
7. Radiological changes

Early as - Soft tissue swelling – Osteoporosis - Acroosteolysis

Late as - joint space narrowing - Acroosteolysis
- Arthritis multilans - Deformities and ankylosis

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