

Proposed Criteria for Early Detection of Leprotic Arthropathy



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Abstract

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 [1]. 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 [2].

Objectives: was the early prediction and diagnosis of leprotic arthropathy among Egyptian leprotic patients & their household contacts.

Patients and methods: Sixty leprotic patients with their ninety- two household contacts who were suffering from musculoskeletal disorders in addition to sixty healthy control subjects were included in this study. full clinical examination, radiological examination , Routine laboratory 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 Cho et al. [3].

Results: wrist, distal interphalangeal (DIP) and metacarpophalangeal (MCP) were highly significantly involved in cases than in other groups ($P < 0.001$). Knees and metatarsophalangeal (MTP) were more prevalent among cases than in other groups with a high significant difference ($P < 0.001$). The mean serum level of AGLI (IgM) antibodies was more among cases and their household contacts than in control groups with a very high significant difference ($p < 0.0001$). The mean serum level of APGLI (A IgG) antibodies was significantly higher among cases and their household contacts than in controls with a very high significant difference $P < 0.0001$

Conclusion: from the previous results we can suggest the following criteria for the early prediction and diagnosis of leprotic arthropathy which might be:

- I. Positive APGL-I (IgM > 0.085 , IgG > 0.0180).
- II. High enthesopathy index > 10 .
- III. Skin manifestations (hypo or hyper pigmented patches).
- IV. Loss of hair especially eye brows.
- V. Arthralgia and / or arthritis in attacks: RA like, or monoarticular.
- VI. Peripheral nerve thickening
- VII. Radiological changes wither early as: -
 - A. Soft tissue swelling
 - B. Osteoporosis
 - C. Acroosteolysis

Or late as:

- i. joint space narrowing
- ii. Acroosteolysis
- iii. Arthritis multilans
- iv. Deformities and ankylosis

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 [1]. Road, et al. [4], stated that, even in countries with developed health services leprosy often diagnosed only in advanced stages of the disease due to;

- I. In most societies, leprosy is not endemic and occurs only as an imported disease of minor public health importance.
- II. Little attention is being paid to teaching leprosy in medical schools. Moreover, chapters of leprosy in general textbooks are not always updated.
- III. 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 [5]. Reports of joint involvement in leprosy have been published since the 1960s [6,7] 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 [8] (Figure 1).

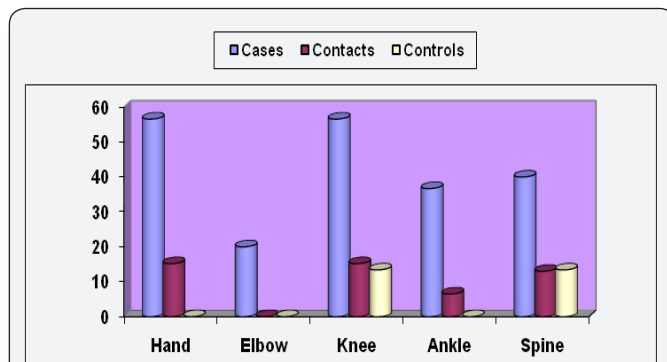


Figure 1: Joints.

0 = Normal

I = Soft tissue swelling

II = Juxt-articular op & j. S.N.

III = Erosions and j. S.N.

IV = Deformity & Ankylosis

V = Charcots joint

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 this 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 ; mean (44.83 ± 4.70). The household contacts were 56 ♂ 36 ♀, their age ranged

from 12-58 years; mean (32.03 ± 11.99) with no family history of leprosy and 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 examination 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 examination, radiological examination, routine laboratory Investigations and serum anti-phenolic glycolipid I (Anti-PGL) which is a unique constituent in the inner layer of mycobacterium leprae cell wall Cho, et al. [3]. The small and large joints were examined from all aspects according to Spread-severity index [9]. Ritchie index [10] was used to assess joint tenderness. Radiological examination: The scoring system for radiographs was done according to Larsen, et al. [11] (Figure 2).

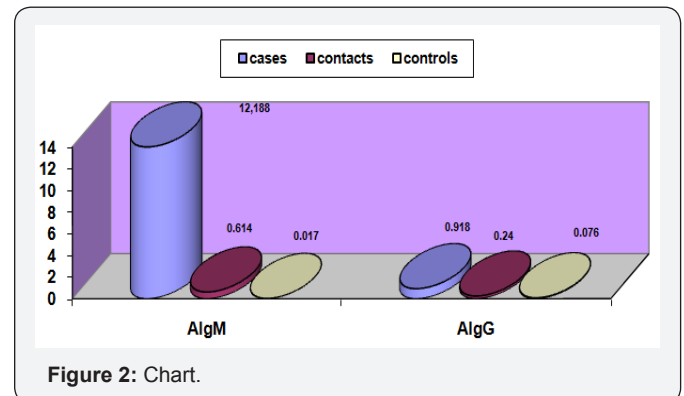


Figure 2: Chart.

Serum samples: 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. [3] with minimal modifications Kazda, et al. [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

Table 1 showed that there was no significant difference in spread severity index between cases, contacts and the control group regarding the tempromandibular, glenohumeral and elbow , hip and subtalar joints where (P>0.05). However the acromioclavicular and ankle joints were significantly more involved among cases than the other groups (P<0.05). The wrist, distal interphalangeal (DIP), metacarpophalangeal (MCP) and the proximal interphalangeal (PIP), knees, and Metatarsophalangeal (MTP) joints were highly significantly involved in cases than the other groups (P<0.001).

Table 1: The percentage distribution of joint involvement for all of the Studied groups according to ss. Index (Balakrishman and Mehra) [30].

		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	

Table 2: The radiological findings for cases, contacts and controls according to Larsen et al. [9].

		Cases		Contact		Control		
		No.	%	No.	%	No.	%	
Hand	Grade 0	26	43.4	90	95.7	60	100	<0.0001
	Grade I	14	23.3	0	0	0	0	
	Grade II	8	13.3	2	15.2	0	0	
	Grade IV	6	10	0	0	0	0	
	Grade V	6	10	0	0	0	0	
Elbow	Grade 0	48	80	92	100	60	100	<0.001
	Grade I	10	16.7	0	0	0	0	
	Grade V	2	3.3	0	0	0	0	
Knee	Grade 0	26	43.4	78	84.8	52	86.6	<0.001
	Grade I	18	30	8	8.7	4	6.7	
	Grade II	8	13.3	4	4.3	4	6.7	
	Grade IV	8	13.3	2	2.2	0	0	
	Grade V	0	0	0	0	0	0	
Ankles	Grade 0	38	63.3	80	93.5	60	100	<0.001
	Grade I	8	13.3	6	6.5	0	0	
	Grade II	10	16.7	6	0	0	0	
	Grade IV	0	0	0	0	0	0	
	Grade V	4	6.7	0	0	0	0	
Spine	Grade 0	36	60	80	87	52	86.6	<0.01
	Grade I	14	23.3	6	6.5	8	13.4	
	Grade II	10	16.7	6	6.5	0	0	

Table 3: The serum level of APGL-1 (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 4: Shows the serum level of APGL 1 (IgG) antibodies in the studied groups.

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

Table 2 showed that the radiological changes of the hand joints were significantly higher among the cases than the other two groups ($P < 0.0001$). Also the radiological changes of elbows, knees, ankle, and spine were significantly higher among cases than in other two groups where $P < 0.001$. Table 3 showed that the mean serum level of APGLI (IgM) antibodies was significantly high in cases and

their household contacts than in control where ($p < 0.0001$). Also Table 4 showed that the serum level of APGLI (IgG) antibodies was also significantly higher in cases and their household contacts than in control groups where ($P < 0.0001$). Table 5 showed that the hypopigmented, hypoesthetic skin rashes were detected more among case than in contacts and control groups $P < 0.001$.

Table 5: Skin manifestations of the studied groups.

	Cases affected		Contacts affected		Controls affected		
	No.	%	No.	%	No.	%	
Hypopigmentation	28	46.7	4	4.3	0	0	< 0.001
Hyperpigmentation	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

Hyper pigmentation and ulcers were significantly more frequent in cases than in the other two groups $P < 0.01$. However there was no significant difference between all of the studied

groups regarding nodules, Raynaud's and urticarial rashes. The erythrocyte sedimentation rate was significantly higher in cases than in contacts and least was among controls $P < 0.0001$ (Table 6).

Table 6: ESR of the studied groups.

	Cases		Contacts		Controls	
	No.	%	No.	%	No.	%
< 20	6	20	26	56.5	28	93.3
20 -	14	46.7	19	41.3	2	6.7
40 -	6	20	1	2.2	0	0
60 -	3	10	0	0	0	0
80 +	1	3.3	0	0	0	0
Total	30	100	46	100	30	100
$X^2 = 44.84$ $P < 0.0001$						
Mean \pm SD	35.47 \pm 18.52		18.28 \pm 10.62		9.20 \pm 6.02	

Discussion

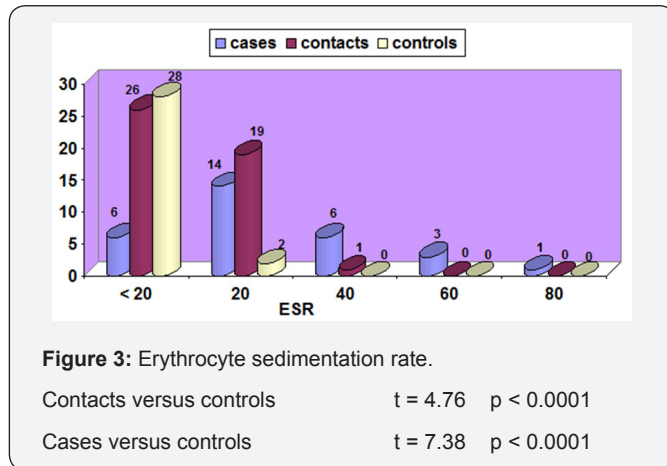
Arthritis is one of the most common leprotic manifestations which may simulate rheumatoid arthritis as stated by Hanafy, et al. [13]. They found that the most commonly involved joints in leprotic arthritis were: elbow (84%), wrist (80%), MCP (80%), PIP (80%), DIP (85%), knee (66%), ankle (72%), TMJ (66%), and MTP (60%). However Karat, et al. [6], stated that a true arthritis may occur particularly in erythematous nodosum leprosum (ENL) which is a reactional 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 diagnosis 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, observed that the elevated levels of anti-phenolic glycolipid I (APGL-I) preceded the clinical diagnosis in most cases, and reported the development of leprosy in two out of eighteen household contacts with persistent seropositivity, and found no cases among 94 household contacts who were persistently seronegative or only transiently positive followed for 30 months [15]. 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 leprosy infection [17]. APGL-I (IgM) was significantly higher among cases than household contacts and control group, ($p < 0.0001$). Also it was higher among household contacts than controls ($p < 0.0002$). 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 where $p < 0.0001$. Also it

was higher among household contacts than control group where $p < 0.0002$ in consistent with studies that done by Hanafy, et al. [13]. Erythrocyte sedimentation rate (ESR) (Figure 3) was significantly higher among twenty eight out of sixty leprotic patients and thirty eight out of ninety two household contacts compared to the control group and this is consistent with the previous study that done by Hanafy, et al. [13].



The serological data of our study revealed a clear age-related correlation with the serum level of anti PGL-I (IgM) among the household contacts only, as agreed Fine, et al. [20]. Overall IgM and IgG levels have been reported to increase during youth and to decrease subsequently with increasing age [21]. 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 [20]. 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. [20].

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 hypergamma-globulinaemia [22] or it may represent Arthur phenomena [23]. So, ESR may be considered as a parameter for disease activity in 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 Hanafy, et al. [13] who reported the same findings with exception of the elbow joint which was involved only in 3.3% in our study compared to 84% in the study which was done by Hanafy, et al. [13]. Among the household contacts, the most commonly involved joint was the knee joint 26% compared to 53.4% among the leprotic patients ($p > 0.05$). Also they reported that the knee joint was involved in 72% among leprotic patients.

Our study highlights that a symmetrical polyarthritis may be a facet of the leprosy infection. As regards the enthesopathic lesions, it was found that the supraspinatus enthesis was significantly involved in leprotic patients than household contacts and control group. lateral epichondylitis 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 be considered as a reactive arthropathy for a well-known pathogen as reported by Inderpal and Surrinder [23].

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 [24].

Radiological examination for 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 Hanafy, 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%). Dinarello [25] stated that IL-1, IL-6 and TNF- α 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 [26].

TNF- α 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 [27]. TNF α together with IL-1 produce juxta articular osteoporosis [28]. Waters, et al. [29] 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 Surrender 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 [18].

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. Hanafy et al 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 ($p < 0.0001$, $p < 0.001$) [13].

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 observed that patients with a positive test for RF in the blood have more severe clinical disease and complications than do seronegative patients [28]. Allen, et al. [30] 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 [31,32].

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. Finally we can conclude that the radiological changes started as 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). Lastly we can suggest the following criteria for early prediction and diagnosis of leprotic arthropathy which might be:

- I. Positive APGL-I (IgM > 0.085, IgG > 0.0180).
- II. High enthesopathy index > 10.
- III. Skin manifestations (hypo or hyper pigmented patches).
- IV. Loss of hair especially eye brows.
- V. Arthralgia and / or arthritis in attacks: RA like, or monoarticular.
- VI. Peripheral nerve thickening

VII. Radiological changes wither early as: -

- A. Soft tissue swelling
- B. Osteoporosis
- C. Acroosteolysis

Or late as:

- i. joint space narrowing
- ii. Acroosteolysis
- iii. Arthritis mutilans
- iv. Deformities and ankylosis

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