

Peripheral Vascular Deficit in Leprosy¹

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Leprosy continues to be one of the major health hazards affecting large population groups in many regions of the world. Though mortality is not a problem, no other disease is so devastating in its ultimate morbid effects as leprosy. Dystrophic changes and mutilations of hands and feet are so common that these are considered more or less part of the symptomatology of the disease. The trophic changes in leprosy have always been attributed to nerve degeneration^(5,6,11). However, it is possible that vascular component is equally important since similar dystrophic changes are seen in certain other diseases⁽¹⁾, like rheumatoid arthritis⁽⁸⁾, scleroderma⁽¹⁴⁾, thrombo-angiitis obliterans (personal observation), where the vascular factor is quite important.

There are conflicting reports regarding vascular involvement in leprosy. Some workers have shown considerable structural and functional damage to vessels^(2,4,9,12,13), whereas Leitner⁽¹⁰⁾ has found normal vessels.

With this background, it was decided to study some leprosy patients in greater detail by angiography and histopathology.

MATERIALS AND METHODS

Thirty-five leprosy patients admitted to Nehru Hospital of the Postgraduate Institute of Medical Education and Research, Chandigarh, India, during the years 1969-1973, were used in this study. All were below 40 years of age. Local and systemic arterial disease was excluded on the basis of detailed physical examination. Diagnosis of leprosy was con-

firmed bacteriologically and by histopathology. Eighteen patients had lepromatous leprosy, ten dimorphous, and seven tuberculoid leprosy.

The arteriographic pattern of hand and foot vessels was outlined by injecting radio-opaque dye (Visotrast "370," sodium salt and methylglucamine salt of the N.N.-diacetyl-3.5-diamino-2.4.6-triodobenzoic acid in aqueous solution) or Conray "420" (sodium calcium edetate and sodium acid phosphate). The brachial artery was exposed in the antecubital fossa while for the feet, percutaneous puncture of the posterior tibial artery was made. Brachial arteriography was done in all patients and both brachial and posterior tibial arteriography were done in one patient. To reduce the vasospasm 0.5 cc of tolazoline hydrochloride (Priscol) or nylidrin hydrochloride (Arlidin) diluted in 10 cc of saline was injected intra-arterially slowly before injecting the contrast material. The dye was rapidly injected by hand-manipulated syringes and four x-ray films were exposed in a serial changer.

From the area of the finger where arteriographic changes were seen, a piece of skin including the subcutaneous tissue as deep as possible was excised and fixed in 4% formaldehyde solution. Paraffin sections were stained with hematoxylin and eosin and Verhoeff's iron hematoxylin stains. The Ziehl-Neelsen technic was followed for demonstration of acid-fast bacilli. Similarly, histopathologic changes in vessels of skin and subcutaneous tissue were studied in postmortem material from nine patients who were below 40 years and died of varying causes other than those in which vascular changes are known. These served as controls.

Skin temperature was recorded with an Ellab Type T.E. 3 thermometer using a skin applicator (Sierex and Co., London) which works on the thermo-couple principle and records temperature differences of 0.1°C. Necessary precautions for skin thermometry were observed. The palmar surface of both the hands over symmetrical areas was utilized. Ten minutes after stabilization of the

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skin temperature, one hand and two thirds of the forearm were immersed in warm water at 43°-45°C. The temperature in the opposite hand was recorded at frequent intervals up to 60 minutes. Skin thermometry and reflex vasodilatation studies were possible only in eight patients.

RESULTS

The majority of patients were males. Only four were females and they had lepromatous leprosy. Most of the patients belonged to a very poor socio-economic status.

Clinical nutritional changes over the extremities in leprosy. Although clinical nutritional changes, i.e., dystrophic changes in the nails, skin and subcutaneous tissue and loss of hair were present in 30 patients (85%) (Table 1), none of the patients had deep ulcerated lesions. Hair loss was seen in 25, dystrophic nail changes in 10, and changes in skin and subcutaneous tissue in 19 patients.

TABLE 1. *Clinical nutritional changes in leprosy.*

| Type | Total no. cases | Hair loss | Nail changes | Skin changes |
|-------------|-----------------|-----------|--------------|--------------|
| Lepromatous | 18 | 15 | 7 | 12 |
| Dimorphous | 10 | 8 | 1 | 6 |
| Tuberculoid | 7 | 2 | 2 | 1 |

Five patients had no such clinical stigmata. Different types of nutritional changes were present irrespective of the type of leprosy.

In all the patients major arterial pulsations were easily palpable; as observed in the radial, ulnar, dorsalis pedis, posterior tibial and peroneal arteries. Vasomotor changes, i.e., Raynaud's phenomenon (25%), impairment of sweating over the extremities (62%), and small old healed trophic ulcers (45%) over the hands and feet were seen frequently. The relative low incidence of trophic ulcers

in this series is accounted for by the fact that patients having normal looking hands and feet were selected for the study where possible.

Arteriographic studies. Arteriographic abnormalities noted in the hand vessels consisted of occlusion, narrowing, tortuosity, dilatation-poststenotic dilatation, irregularity and incomplete filling of the lumen by radio-opaque material. These changes were studied separately in the vessels of wrist and palm and their palmar digital branches. Two arteriograms were unsatisfactory for detailed analysis and were excluded.

Table 2 shows that occlusion, narrowing and tortuosity were seen in 91%, 85%, and 72% respectively, of the 33 arteriograms studied. Irregularity of the lumen was very common and was noted in one or the other vessel in all the arteriograms. The ulnar artery was more frequently involved (74%) than the radial (50%) (Fig. 1). Superficial and deep palmar arches were involved in 56% and 42% of the arteriograms. In the area of the hypothenar eminence increased vascularity was noted in four arteriograms but clinically the overlying skin was normal. However, in two of these patients there was marked wasting of hypothenar muscles. Another interesting feature was the presence of an increased number of small vessels over the base of the fifth metacarpal in 42% of the arteriograms (Fig. 2). Similar changes have been noted by previous workers in other small vessel disorders.

Table 3 shows that in palmar digital vessels, occlusion, narrowing and irregular lumen of more than two vessels was seen in 82% and 79% of the arteriograms (Fig. 3). Arcuate vessels run from one palmar digital artery to the opposite side. They are seen normally, but their exact number has not been described. In clinical arteriography their presence is suggestive of vascular insufficiency. In this study arcuate vessels were seen maximally in the region of the index

TABLE 2. *Number of arteriograms associated with a given number of vessels showing abnormalities in wrist and palm.*

| Type of abnormality | Number of vessels with abnormalities | | | | | |
|---------------------|--------------------------------------|-----|-----|-----|-----|-------------|
| | Nil | 1-2 | 3-4 | 5-6 | 7-8 | More than 8 |
| Occlusion | 3 | 17 | 7 | 4 | 2 | nil |
| Narrowing | 5 | 13 | 8 | 6 | 1 | nil |
| Tortuosity | 6 | 9 | 2 | 6 | 9 | nil |

TABLE 3. Number of arteriograms associated with a given number of vessels showing abnormalities in palmar digital vessels.

| Type of abnormality | Number of vessels with abnormalities | | | |
|---------------------|--------------------------------------|-----|-----|-------------|
| | Nil | 1-2 | 3-4 | More than 4 |
| Occlusion | 2 | 4 | 8 | 19 |
| Narrowing | nil | 7 | 6 | 20 |
| Irregular lumen | 2 | 7 | 7 | 17 |

finger (58%) and next in the thumb region (50%). In some patients arcuate vessels served as collaterals and showed retrograde filling of the opposite digital palmar artery (Fig. 4).

In the arteriograms of the feet, similar changes were noted and also showed retrograde flow of contrast material from the posterior tibial into dorsalis pedis artery (Fig. 5).

Histopathologic changes. These changes



FIG. 1. Left hand angiogram of a BB patient showing occlusion of ulnar artery, deep palmar arch, palmar metacarpal arteries and palmar digital arteries of fingers. *Princeps pollicis* artery is poorly outlined; *radialis indicis* artery is occluded. Medial palmar digital branch of thumb is tortuous.



FIG. 2. Right hand angiogram of a LL patient showing irregular lumen and poststenotic dilatation of ulnar artery. *Princeps pollicis* artery is blocked approximately one centimeter away from its origin from radial artery. Increased number of small vessels are seen at the base of fifth metacarpal. Superficial palmar branch of radial artery shows irregularity of the lumen with tortuosity and stenosis at its origin from the radial artery.

were present in the arteries, arterioles, capillaries and venules in 16 patients (47%), predominantly those having the lepromatous variety of the disease. The arterial changes noted include intimal thickening and organizing thrombi causing marked narrowing of lumen (Fig. 6). Occluding thrombi with evidence of recanalization were noted in five, and interruption of internal elastic lamina in two cases. The media of small and medium sized arteries showed hypertrophy in four and associated fibrosis in one (Fig. 7); while periarteritis was noted in seven, and endothelial proliferation in the smallest size arteries was present in one case. Arteriolar changes seen were endothelial proliferation and endarteritis obliterans. Capillaries



FIG. 3. Left hand angiogram of a BB patient showing tortuosity and irregular lumen of the palmar digital arteries of index finger. Medial palmar digital artery of index finger shows dilatation before its termination near the tip of distal phalanx. Two prominent arcuate vessels crossing the front of proximal and middle phalanx of index finger are seen. Pulp venous phase is absent in index finger and normal in thumb. Palmar digital arteries of middle finger are occluded.

showed proliferation of endothelial cells. In one lepromatous case, a venule was completely occluded by an organizing thrombus (Fig. 8). In the control series of nine patients below 40 years who died of various causes other than arterial disease, the histopathologic changes in the vessels were minor and less frequent. Mild hypertrophy of the media



FIG. 4. Right hand angiogram of a LL patient showing only distal part of *radialis indicis* artery which is refilled by an arcuate artery from medial palmar digital artery of index finger. Irregularity of the lumen of both the digital arteries is also seen.

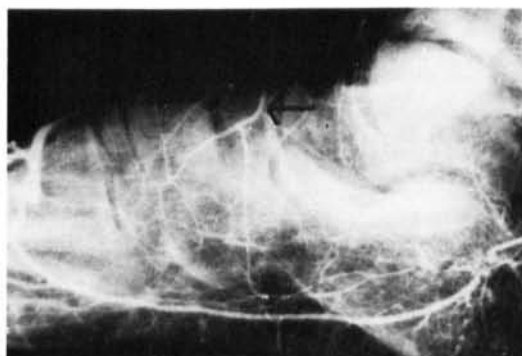


FIG. 5. Left foot angiogram of a LL patient showing retrograde flow of contrast material into *dorsalis pedis* artery from the posterior tibial artery. Lateral tarsal artery (shown by arrow), a branch of *dorsalis pedis* artery, is also visualized.



FIG. 6. Section of skin from finger of a LL patient. A small artery shows an organized thrombus with reduplication of elastic membrane. There is adventitial fibrosis. Verhoeff's Iron Hematoxylin, X100.

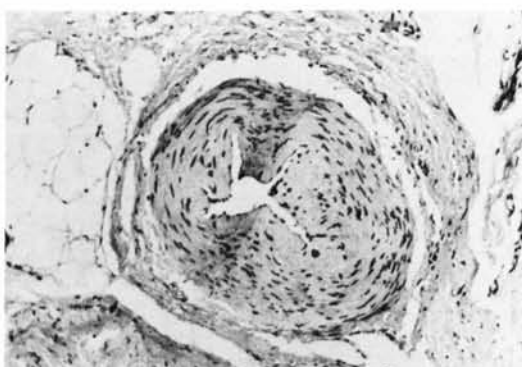


FIG. 7. Section of skin from finger of a LL patient. A small artery shows marked medial hypertrophy with narrowing of the lumen. There is increased fibrosis and minimal inflammatory reaction in the periarterial zone. H & E, X100.

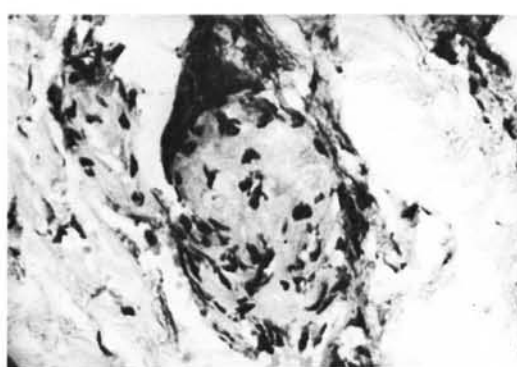


FIG. 8. Section of skin from finger of a LL patient. A small venule shows complete obliteration of the lumen as a result of endothelial proliferation with organized thrombus. H & E, X100.

was seen in three specimens and a large vessel showed eccentric intimal thickening in one out of nine autopsies.

Reflex vasodilatation was absent in all three patients having dimorphous leprosy, while it was normal in two and impaired or absent in three patients having lepromatous leprosy.

The degree of clinical nutritional changes and of arteriographic and histopathologic changes were arbitrarily graded into mild, moderate and severe. There was no correlation between the clinical, histopathologic and arteriographic changes. There was no predilection for any form of leprosy to show arterial changes more than others.

DISCUSSION

All the 35 leprosy patients studied were below 40 years of age. It is hoped that occult arteriosclerosis obliterans did not vitiate our findings because it is uncommon for arteriosclerosis to develop below this age and in the type of vessels studied. Patients with normal looking hands and feet were preferred for the study because chronic inflammatory reaction in the vicinity of deformed and mutilated fingers and toes may lead to secondary vasculitis.

Clinical signs of vascular insufficiency such as dystrophic changes in nails, skin and hair are undependable in the context of leprosy as these are well known features of leprosy itself. Though these changes were seen

in 85% of the patients, they cannot be confidently called signs of vascular insufficiency. Under the circumstances, arteriography was of great value in showing the changes in the arterial tree. A successful delineation of major arterial channels of the wrist, hand and digits were obtained by brachial arteriography. It is interesting to emphasize that some form of arteriographic abnormality was seen in all of these contrast studies. In the wrist and palm more than two major vessels of the ulnar, radial or palmar arch group showed occlusion in 91%, narrowing in 85%, and abnormal tortuosity in 72%.

More than four vessels showed irregular lumens in most of the arteriograms.

The ulnar artery was more often involved than the radial artery. This is the pattern in thrombo-angiitis obliterans also. However, the reason for this finding in these two arterial diseases is not clear. In about half of the arteriograms, increased vascularity and neovascularization was seen at the base of the fifth metacarpal. The exact cause of this finding is also not clear. It is unlikely to be secondary involvement as there was no ulceration or induration over the hypothenar eminence.

Palmar digital vessels showed more than two vessels occluded in 82% arteriograms, the fingers were more often involved than the thumb. Whether this finding is related to more frequent involvement of the ulnar artery than the radial is conjectural. Narrowing of more than two digital vessels was seen in 79%. This is in contrast to Paterson's⁽¹²⁾ observation. He noted similar findings in only one-fourth of the arteriograms in a study of 12 patients. Irregularity of the lumen in more than two digital vessels was seen in 74% of our visualizations.

Arcuate vessels crossing in front of the digits are seen normally but are small and sparse. In the present study the arcuate vessels were seen more often and in some arteriograms they were certainly serving as collateral channels because retrograde filling of the digital arteries via these vessels was documented. The study of pulp capillary and venous phase was not very reliable in the present study. In the absence of a very sophisticated rapid cassette changer, the limited number of films taken might have affected the findings.

Some data is available in connection with

various angiographic abnormalities in leprosy, but most of the workers have limited their attention to palmar digital vessels^(3, 4, 7, 12). To the best of our knowledge, involvement of radial and ulnar arteries or their major branches at the level of wrist and palm have not been studied in detail. Vascular occlusion and narrowing of palmar digital vessels have been described and some workers have mentioned the presence of arteriovenous shunts. The latter were not seen in the present study. Absence of pulp capillary and venous phase and other minor abnormalities described by other workers cannot be commented on because of technical difficulties in studying these aspects.

Though only one foot arteriogram was studied there is no reason to believe that the changes in the foot vessels are likely to be any way different from those described in the hands.

Another method of studying the integrity of the vascular reflex is by the reflex vasodilatation technic. In cases of leprosy where neuropathy is constant, some of the arterial changes could be attributed to this factor. In the present study, the phenomenon of reflex vasodilatation was absent in all dimorphous patients but normal in two, and impaired or absent in three lepromatous patients. This may be due to a varying degree of involvement of sympathetic nerve fibers in the different types of leprosy. Barnetson⁽¹⁾ found reflex vasodilatation abnormal in late, and normal in early cases of leprosy. He also noted that exceptions do exist.

Histopathologic vascular changes were noted in 47% of cases but their actual incidence is higher for the following reasons: a) since our biopsy material scarcely measured 0.25×0.25 cm, scattered vascular changes may not be seen in the small biopsy; b) the site of biopsy was skin and subcutaneous tissue and not the main palmar digital artery which showed the arteriographic abnormalities. Histopathologic changes cannot be considered independently of the arteriographic changes because biopsy is not likely to pick up large arteries. Obviously, histology and arteriography are supplementary to each other. When the findings of these two methods are combined, it is evident that vascular involvement in this group of young leprosy patients is due to leprosy. Whether, in addition, vasopastic and autonomic processes

play some role, as they do in Raynaud's phenomenon, rheumatoid arthritis and other diseases, is not clear.

These arteriographic and histopathologic studies have thus demonstrated the frequent presence of vascular changes in small and large size arteries, arterioles, capillaries and venules. These changes must play an important role in contributing to the mutilation and deformities of hands and feet in leprosy.

SUMMARY

There is considerable controversy regarding the frequency and significance of vascular lesions in leprosy. Thirty-five patients of leprosy under 40 years of age, without any local and systemic arterial disease, with normal looking hands and feet, were subjected to brachial arteriography. One patient also had posterior tibial arteriography. Diagnosis of leprosy was confirmed by bacteriologic and histopathologic techniques. Biopsy material was studied from the area of radiographic abnormality, similar material was obtained from nine matched control subjects at autopsy. Skin thermometry and reflex vasodilatation were studied in eight cases. Various fractions of serum lipids and cholesterol were estimated in all patients and found to be within normal range. Arteriographic abnormalities such as occlusion, narrowing, tortuosity, dilatation, poststenotic dilatation, irregularity and incomplete filling of the lumen by radio-opaque material, were seen in more than two vessels in 50% of the arteriograms in wrist and palm; digital vessels showed abnormality in 75% to 94% of cases. The ulnar artery was more frequently involved (74%) than the radial (50%). Superficial and deep palmar arches were equally affected. Increased vascularity in hypothenar eminence area was seen in three arteriograms. Marked increase in arcuate vessels was noted in 60% of patients. Some arcuate vessels were serving as collaterals. Histologically, all grades of vessels including capillaries showed changes in nearly half of the patients. Reflex vasodilatation was lost in three patients of dimorphous leprosy, and impaired or absent in three of five patients of lepromatous leprosy. There was no predilection for any form of leprosy to show arterial changes more than others. This study clearly demonstrates that the vascular involvement in leprosy is very frequent and must be playing an important role in causing

mutilations and deformities of hands and feet.

RESUMEN

Hay considerable controversia con respecto a la frecuencia y significancia de las lesiones vasculares en lepra. A 35 pacientes de lepra con menos de 40 años de edad, sin ninguna enfermedad local o sistémica, con manos y pies de aspecto normal, se les hizo un estudio de arteriografía braquial. A uno de los pacientes, también se le hizo una arteriografía tibial posterior. El diagnóstico de lepra se confirmó por medio de técnicas bacteriológicas e histopatológicas. El material de biopsia se estudió desde el aspecto de anormalidad radiográfica, obteniéndose un material similar, como control, de la autopsia de 9 sujetos comparables. Se estudió en 8 casos la termometría de la piel y la vasodilatación refleja. En todos los pacientes se determinaron los índices de colesterol y lípidos del suero, y se encontraron dentro de límites normales. Se encontraron anomalías arteriográficas tales como oclusión, estrechamiento, tortuosidad, dilatación, dilatación postestenótica, irregularidad y llenado incompleto del lumen por material radio-opaco, en más de dos vasos en el 50% de los arteriogramas de muñeca y palma; los vasos digitales mostraron anomalías en 75% a 94% de los casos. La arteria cubital (74%) estaba afectada con mayor frecuencia que la radial (50%). Los arcos palmares superficiales y profundos estaban afectados en la misma forma. En tres arteriogramas se observó vascularidad aumentada en la eminencia hipotenar. En 60% de los pacientes se encontró vasos arcuados. Algunos de los vasos arcuados servían como colaterales. Histológicamente, todos los tipos de vasos, incluyendo los capilares, mostraban cambios en casi la mitad de los pacientes. La vasodilatación refleja estaba perdida en tres pacientes con lepra dimorfa, y disminuida o ausente en 3 de 5 pacientes con lepra lepromatosa. Las alteraciones arteriales no mostraron predilección por alguna de las formas de lepra más que por las otras. Este estudio demuestra claramente que el compromiso vascular en lepra es muy frecuente y que debe estar jugando un papel importante en la producción de mutilaciones y deformidades de manos y pies.

RÉSUMÉ

La fréquence et la signification des lésions vasculaires dans la lèpre est fort controversée. On a procédé à une artériographie brachiale chez 35 malades de la lèpre âgés de moins de 40 ans, exempts de toute affection artérielle locale ou systémique, et qui présentaient des mains et des pieds d'aspect normal. Un malade a également subi une artériographie tibiale postérieure. Le diagnostic de lèpre a été confirmé par des examens bactériologiques et histopathologiques.

On a procédé à des biopsies dans les endroits présentant des caractéristiques anormales, du matériel de biopsie semblable étant obtenu chez neuf sujets témoins comparables après autopsie. Chez huit cas, on a étudié la thermométrie de la peau et la vasodilatation réflexe. Les diverses fractions des lipides sériques, de même que le cholestérol, ont été mesurés chez tous les malades. Les valeurs observées se situaient dans les limites normales. Dans 50% des artériographies pratiquées au niveau du poignet et de la paume, on a relevé, dans plus de deux vaisseaux des anomalies artériographiques telles que occlusions, rétrécissements, aspects tortueux, dilatations, dilatations poststénotiques, irrégularités, et remplissage incomplet de la lumière par du matériel radio-opaque. Les vaisseaux digitaux ont présenté des anomalies dans 75% à 94% des cas. L'artère cubitale était plus fréquemment atteinte (74%) que l'artère radiale (50%). Les arcades palmaires superficielle et profonde étaient atteintes dans la même mesure. Dans trois artériographies, on a constaté une augmentation de la vascularisation de la zone de l'éminence hypothénar. Une augmentation notable des vaisseaux de l'arcade a été relevée chez 60% des malades. Certains de ces vaisseaux servaient comme collatéraux. Chez près de la moitié des malades les vaisseaux, quelles que soient leur dimension, y compris les capillaires, ont montré des modifications histologiques. La vasodilatation réflexe était perdue chez trois malades atteints de lèpre dimorphe, et endommagée ou absente chez trois des cinq malades souffrant de lèpre lépromateuse. On n'a constaté aucune relation entre la présence de modifications au niveau des artères, et la forme de lèpre, aucun type de lèpre n'étant plus exposé aux risques de montrer de telles modifications. Cette étude montre clairement que l'atteinte vasculaire dans la lèpre est fort fréquente, et qu'elle doit jouer un rôle important dans l'étiologie des mutilations et des difformités des mains et des pieds.

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