Leprosy: Immunopathology, neurologic Mand"estateons and Treatment

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Introduction

Leprosy caused by Myobacterium leprae, an acid-fast bacillus is a chronic infection affecting skin and peripheral nerves. Myobacterium leprae was first identified by G. Armauer Hansen in 1873.1 It is a significant cause of morbidity in endemic areas. Peripheral neuropathy is a common manifestation of the disease and involves dermal and superficial peripheral nerves. The pathologic expression of diseases depends on the host response to M. leprae and ranges from tuberculoid leprosy to lepromatous leprosy.'- The latency of the infectioe agent poses a challenge for diagnosis and long-term management especially in patients with pure neuritic form without skin lesions. Leprosy reaction is as important cause of neurologic disability in established patients. The diagnosis should be considered in patients from endemic areas presenting with peripheral neuropathy with or without skin lesions."-

Epidemiology

The vast majority of leprosy is found in tropics and subtropics of Asia, the south pacific: and Africa. Children appear to be at greater risk than adult contacts, although most childhood cases remit spontaneously. The age related incidence is bimodal with peaks between 10 and 14 years, and 30 and 60 years. The incubation period is estimated to be 2 to 7 years?,3

It is generally accepted that humans acquire the disease from skin-to-skin contact or through nasal secretions of infected individuals. Leprosy is still prevalent in many areas of the world particularly in tropical and developing countries, where 10 million people are affected.

Immunopathogenesis

Leprosy is caused by a single microorganism, however differences in the host Susceptibility to infection result in marked differences in the severity of disease expression. Clinical spectrum of leprosy is broad and current classifications recognize three major forms of the disease: tuberculoid, lepromatous, and borderline leprosy.3 Patients with tuberculoid leprosy have a high resistance to infection and develop an intense immune reaction that reduces the

proliferation of microorganisms, but causes acute peripheral nerve and skin damage that is usually circumscribed. In contrast patients with lepromatous leprosy do not mount an adequate immune reaction and microorganisms disseminate through the body and damage to peripheral nerves is not as acute as in tuberculoid leprosy but the lesion is more generalized and the skin lesions are more severe.`t Patients with borderline leprosy have an unstable immune reaction to the infection, resulting in a disease that may have characteristics of the two other types of leprosy.

Clinicopathologic Classifications by Ridley and Jopling

Classification proposed by Ridley and Jopling can be divided into five subtypes based on histologic and immunologic features.¢ tuberculoid (TT), lepromatous (LL), borderline tuberculoid (BT), mid borderline (BB) and borderline lepromatous (BL).

In tuberculoid leprosy, the cell-mediated immune reaction results in epitheliod granuloma at the portal of entry usually the skin, the chest, or upper limbs. The granuloma is seen as a well-defined, hypopigmented, anesthetic skin lesion with a distinctly delineated raised border. Biopsy of these lesions fails to demonstrate the causative agent in most cases. Peripheral nerve involvement is usually limited to one nerve that appears enlarged and is palpable.'-

In lepromatous leprosy microorganisms enter the bloodstream, disseminate through the body, and may lodge in almost every organ, including the brains In this form of the disease skin and peripheral nerve involvement is diffuse, resulting in numerous papular and macular skin lesions as well as in symmetric affection of peripheral nerves with a marked predominance for small sensory fibers. Biopsy of skin lesions usually shows abundant microorganisms. 1M. leprae replicates in body areas where the temperature is low (e.g., skin, distal peripheral nerves, anterior chamber of the eye, testes, and upper respiratory tract).

Borderline patients have the highest potential to develop neurologic complications. Their cell mediated immune response may become deficient to allow the mycobacterium to be more widely disseminated at warmer sites than in tuberculoid cases. The bacilli ultimately provide a sufficient stimulus to evoke a significant inflammatory response and the patient may develop multiple rnononeuropathies not typically seen with other forms of disease such as brachial plexus or median nerves at the elbow. Caseation does not occur in borderline cases although enlargement of peripheral nerves may occur.

Neurologic manifestations

Superficial Neuropathy

Intracutaneous nerves and superficial portions of peripheral nerve trunks are involved in this process, while nerves in deeper tissues are spared. Dermal nerves are invaded first leading to diminished sensitivity to temperature, touch, pain and pressure with loss of sweating. 6

Peripheral Nerve Involvement in tuberculoid Leprosy

Skin lesions consist of hypesthetic macules that are few in number and asymmetric in distribution. Superficial nerve fibers are always affected and may be palpable. Sensory loss is earliest for pain and temperature. The ulnar, median, peroneal, and facial nerves are especially prone. The superficial cutaneous radial, digital, posterior auricular, and sural nerves are commonly affected. Painful nerve abscesses with caseation can form and axonal loss is prominent.'---

Peripheral Nerve Involvement in Lepromatous Leprosy

Skin lesions are more numerous, pleomorphic and symmetric, and have a characteristic distribution. The ear lobes and helices usually are affected, and other lesions tend to occur on dorsal surface of hands, dorsomedial forearms, dorsal feet, and anterolaterai aspects of legs. There may be normal sensation in skin lesions and enlarged nerves ma,' be functionally normal. At later stages, infected nerve trunks lose function, partly as a result of repeated trauma and partly because of the pathologic process. The ulnar nerves are usually the first to be affected. Nerve caseation and abscess formation do not occur in lepromatous leprosy. ,

Cranial nerves involvement

Cranial Nerves V and VII are most corn9ronh-involved in leprosy.$, Cranial nerves VIII, IX and X has been occasionally reported.S Leprosy should be considered as differential in patients presenting with multiple cranial neuropathies. Olfaction and vision may be injrired by bacillary infiltration of the end organs. Blindness may also result from keratitis via a combination of weak eye closure and corneal anesthesia.

Pure neuritic form without skin lesions

This is more frequently described in Southeast Asia and India.'-6 Virtually all of the cases are tuberculoid or borderline tuberculoid. A thickened nerve at a site o predilection may serve as an important diagnostic clue. Althou„h visible skin lesions are absent, the intracutanCOU-S nerves can be involved. An excisional skin biopsy with inclusion. of subcutaneorus tat from an anesthetic area may be diagnostic. Nerve biopsy may also be considered it' skin biopsy is unrevealing.

CNS Leprosy

In one study 25% of leprosy patients older than 65 years had clinically overt dementia, a prevalence that was four times higher than that reported in an age-matched. In patients with leprosy, pathologically confirmed cases of

Alzheimer's disease outnumber those of vascular dementia. Another study showed that the prevalence of dementia in leprosy is lower in patients who received continued therapy than in those treated interinittently.l0 The pathogenetic mechanisms explaining a cause-and-effect relationship between leprosy and dementia are not fully understood.

Leprosy Reactions

1. Reversal reactions: These occur in dimorphous and tuberculoid leprosy." Pre-existent skin lesions become red and swollen and reaction may follow the institution of effective chemotherapy and is caused by increased activity of immunologically competent cells. Although the development of higher resistance is a favorable response, peripheral nerves may be damaged in the process. 12

2. Erythema nodosum leprosurn: This occurs in lepromatous leprosy and is characterized by high fever, prostration, and crops of painful nodules in regions where bacilli numbers are -reatest l s Acute painful mononeuritis and mononeuritis multiplex may occur.

Testing for Neuropathy

Electrodiagnostic Tests

Electrodiagosdc studies confirm the presence of the individual mononeuropathies or mononeuropathy multiplex in leprosy. Affected nerves often demonstrate both axonal and dernyelinatina features.t Nerve conduction studies commonly shows evidence of segemental slowing in motor nerves or low sensory amplitudes in clinically involved nerves. Abnormalities may be found in asymptomatic nerves or across segments of nerves that show focal thickening. 1 '5

In ulnar nerve conduction slowing usually occurs at the elbow. Median slowing localizes to the distal portion of the forearm rather than the carpal tunnel. In the peroneal nerve impaired conduction can be demonstrated in the segment between the poplitcal fossa and fibular head. Posterior tibial nerve conduction is slow from the knee to ankle. Facial nerve latencies are prolonged or totally absent in patients with lagophtthalornos.

The presence of axonal involvement can be demonstrated by needle EMG with evidence of positive sharp waves, fibrillations and large polyphasic motor units present in involved muscles.

Treatment .

	WHO	Hansen's Disease Centre
Pauci bacillary	dapsone 100mg daily Rifampin 600mg montly Duration-6 months	dapsone 1 OOmg daily rifarnpin 600mg daily dapsone 1 OOmg dadti
Multibacillary	dapsone 100mg daily Ciofazimine 50rng daily Rifampin 600m- monthly. Duration: minimum 2 yrs or until skin smears negative	dapsone 100mla daily clofaznnme 50rng daily rilampin 600mg daily duration:2 yrs or mail skin smears negative
Dapsone resistance		ciofaziminc 50mg dark
Or G6PD deficiency		riiampin 600mg daily Consider adding: Olloxacin 40Om,. daiiv- Cairithomycin 250mL twice daily or Minocychnc 100mg :fail,,

Monofilament sensitivity test

Nylon filaments with varying tensile strengths ranging from 4.17 to 6.10 units corresponding to measured force of I g to 75 g, are applied to the plantar surface of the toes and feet at various points. Birk and Sims established that patients who no longer feel a i01-)filament were at (ratter rIsk for developing foot ulceration.°

Diagnosis - Tuberculoid Leprosy

The key to diagnosis s a cli lic~t!

suspicion. Diagnosis may be confirmed with the lepromin test6, the results of which usually are positive, and a biopsy of the skin lesion. Sometimes it may be difficult to select an appropriate site for biopsy. A useful test is a thermal sweat test, with charting of the areas of anhidrosis. One of these areas may then be biopsied. Where a well-demarcated maeule is present, the biopsy site of choice is the edge of the lesion . Pathologic changes are those of an epithelioid granuloma. Caseation may be present. Langhans' and foreign-body giant cells may be seen, but acid-fast bacilli tend to be scanty. 7 Slowing of nerve conduction parallels the distribution of the lesion, and since the distribution of nerve involvement is quite asymmetric, comparison of findings on the opposite limbs is sometimes helpful.

Diagnosis - Lepromatous Leprosy

Diagnosis is based on the clinical features of skin lesions of characteristic distribution and mononeuritis multiplex pattern of nerve involvement and is confirmed on tissue examination of the ear lobe. 7 The lepromin test result is usually negative. The nerve trunk enlarges in a fusiform shape. There are large numbers of foamy macrophages, mast and plasma cells and large numbers of the bacilli are present. Myelinated fibers are diffusely reduced in number, and on single teased fiber examination, the predominant abnormality is that of segmental demyelination, although in advanced cases axonal degeneration may be prominent. 17

Diagnosis - Borderline Leprosy

In borderline leprosy the nerve biopsy shows poorly defined granuloma and bacilli can be seen towards the lepromatous end of the spectrurn. 7

The nerve biopsy is seldom necessary to diagnose leprosy. It will be most useful in pure neuritic leprosy ill which no slain lesions are present. The nerve pathology shows tuberculoid or borderline featU!_CS ill pure neuritic leprosy.

Helnolysis is not uncommon with dapsone, but the anemia if present is mild and seldom requires discontinuation of the drug. Clofazimine pigments the involved skin, giving a red-to-black coloration. Rifalnpins major side effect is hepatotoxicity, which fortunately is uncommon. It also accelerates the hepatic metabolism of several drugs such as prednisone and oral contraceptives.

Treatment of Leprosy Reactions

Leprosy reactions must be treated promptly. Prednisone. thalidomide and clofazirnine are the recommended drugs. Type I or reversal reactions are treated with prednisone 60 to 80 ing/d. 11 Type ? reactions or erythema nodosum leprosum, may require only sflnptoinatic treatment if they are mild. Severe reactions are treated with thalidomide 300 to 400 mg/d.l 3 1 S Because of its terato--enic effects, reliable contraception must be provided to women of childbearing age. The acute mononeuritis is treated with systemic corticosteroids and splinting. Surgical treatment (e.g., decompression or splinting) may need to be considered.

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