Leprosy: A disease with diagnostic and management challenges!

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Accurate diagnosis of leprosy is of elementary importance to all aspects of the disease including epidemiology, case management and the prevention of disabilities. Delays in the diagnosis of leprosy are not uncommon and misdiagnosis is more common in non-endemic countries where the disease is rare. The long incubation period, variable clinical presentations and waning expertise about the disease are the likely reasons for a delay in diagnosis. Diagnosis and classification of leprosy have traditionally been based on the clinical examination and frequently with additional information from skin smears. Histopathologic examination, inoculation of the mouse foot pad, serologic tests and polymerase chain reaction (PCR) tests have been largely confined to research studies, but attempts are being made to develop new tools that will make the tasks of diagnosis and classification easier and more reliable. Three cardinal signs have remained the basis for the clinical diagnosis of leprosy:

a) Anaesthetic/ hypoanesthetic skin lesion(s)
b) Thickened peripheral nerve(s) with impairment of sensations in the area supplied
c) Acid-fast bacilli in the skin smear

Any one of these signs has been regarded as sufficient for the diagnosis of leprosy, so that the sensitivity is high. Each sign is also quite specific in itself so the specificity is also high. The most important potential source of error is the reliability of the examination of an individual patient, by uninitiated health workers.

As the clinical management of leprosy is becoming integrated into the general health services, majority of the patients will be diagnosed and managed by non-specialists. Therefore, attempts have been made to simplify the guidelines for diagnosis to be used by field staff taking into account a single sign – the finding of the skin patch or patches with definite impairment of sensations. Others with lesions suggestive of leprosy but without anesthesia or not diagnosed by this single criterion may be referred to an appropriate center for further examination. This diagnostic strategy being routinely applied in surveys and many national programs may lead to significant under diagnosis, particularly of multibacillary disease (MB) where sensations remain almost intact in the early stage of the disease. This can have serious epidemiological and clinical implications. Firstly, MB patients are the major source of infection leading to further transmission of M. leprae and secondly they are at greater risk of reactions and consequent nerve damage. Delay in diagnosis may result in preventable disabilities with the accompanying psychosocial sequelae. Over diagnosis on the other hand will result in needless treatment, but, more important are, the damaging psychosocial consequences of the diagnosis of leprosy.

The WHO classification of disease based on number of skin lesions has conspicuously ignored the number of peripheral nerve trunks involved. The obvious reason could be the lack of adequate experience and proficiency among field workers to palpate and identify the thickened peripheral nerve trunks. Nevertheless, this can have serious implications in PB patients having ≥2 peripheral nerve trunks involved especially in different limbs. It is likely that such PB patients classified solely on number of skin lesions have widespread/disseminated disease and are being inadequately treated with PB regimen and therefore actually being under treated. There is paucity of data on this aspect and future studies are desired to address
this issue. Laboratory based time tested tools such as slit skin smear and histopathology are sidelined as they are regarded as not very practical or do not add on to the sensitivity of diagnosis. There is no surveillance system to record the number of relapses occurring in the community especially after introduction of short term fixed MDT multibacillary regimens. In addition there is no recording and tracking system in place to access the patients who discontinue their treatment. This poses a public health risk due to the likelihood of infectiousness of active relapses and treatment defaulters.

**SKIN LESIONS WITH SENSORY IMPAIRMENT**

Hypopigmented or erythematous patches/plaques are often the first clinical sign of the disease in many newly diagnosed leprosy patients. Since many other conditions produce similar lesions, it must be accompanied by definite sensory loss to be specific for leprosy. This greatly reduces the sensitivity of this sign, especially in MB cases where lesions are less distinct and less likely to be anesthetic.

In a well designed study carried out in Malawi, sensory examination was done in histopathologically proven paucibacillary (PB) lesions. The sensitivity and specificity of the loss of touch sensation in a lesion as a diagnostic test was 48.5% and 72% respectively.[3] In other published studies, higher figures for the sensitivity of this test among PB patients were reported; 93% in India,[4] 92% in Bangladesh[5] and 86% in Ethiopia.[6] This difference could be due to the varied duration of the disease at the time of examination. However, specificity was not calculated in these studies. It has been seen that some hypoaesthetic lesions are occasionally seen in conditions other than leprosy such as chronic dermatitis producing thick lichenified skin lesions, which may lead to some degree of over diagnosis. Other skin lesions without sensory loss can also be confused with some common dermatoses resulting in misdiagnosis. In field conditions, erythematous plaque lesions of leprosy may be labeled as tinea, psoriasis, lupus vulgaris etc. and hypopigmented patches are often confused with pityriasis alba, pityriasis versicolor, and vitiligo etc.

Very few studies have examined anaesthetic lesions in MB cases, because there is less apparent difficulty in the diagnosis, using the traditional cardinal signs, including skin smears. Published figures for the sensitivity of anaesthesia in skin lesions in MB patients are almost similar i.e. 49% in Bangladesh[5] and 54% in Ethiopia.[6] In Ethiopia, the sensitivity of this single criterion was 70% for all patients. Notably a large proportion (74%) of those whose lesions were not anaesthetic were smear-positive, and therefore, represented potential source of M. leprae in the community.[6] It implies that utilizing anesthesia over the skin patches as the single criterion, almost 30% of leprosy patients may be missed, most of whom will be smear positive.[2]

**PERIPHERAL NERVE TRUNK THICKENING**

In the early phase of MB disease the nerves are not grossly thickened and may be passed of as normal, but in established disease thickened nerves are more commonly seen in MB than among PB patients. Thickened nerves were found in a greater proportions of new cases in Ethiopia (ulnar nerve in 68%),[6] where the patients often present late, than in India (ulnar nerve in 23%),[7] where detection is generally much earlier. Reported figures for nerve enlargement in MB and PB patients from Bangladesh are 96% and 86% respectively,[3] whereas in Ethiopia, the corresponding figures were 91% and 76%.[6] In a study of early MB patients from India, only 20% patients had enlarged nerves.[4]

The reproducibility and specificity of the examination for nerve enlargement have been questioned.[8] A study from India found only moderate reproducibility among eight experienced paramedical workers.[9] False positive findings may occur because of poor examination technique or because of non-specific enlargement of a nerve seen in some heavy manual workers.[8,10] On the other hand some diseases and conditions with nerve thickening (hereditary sensory motor neuropathy, Dejerine – Sotta syndrome, amyloidosis, and neurofibromatosis) or without nerve thickening (diabetic, alcoholic neuropathy, lead/arsenic toxicity, and vitamin B deficiency) may simulate leprosy like sensory loss with or without deformities, paralysis, trophic ulcers etc.

Neuritic leprosy presents as peripheral neuropathy in which there are no skin lesions suggesting leprosy. The diagnosis depends on finding definite nerve enlargement with nerve function impairment. In Ethiopia, the diagnosis was made in 0.5% of newly detected cases,[12] whereas in India 4.2% of newly
detected cases exhibit this form of disease.[13] In Nepal, 8.7% of new patients in the field were found to have neuritic leprosy.[14] These patients would be diagnosed by the classical cardinal sign of peripheral nerve enlargement but not by the single criterion of an anaesthetic skin patch. There are no defined guidelines by WHO about the classification and treatment of these cases depending upon number of nerves involved. Experienced leprologists however, would treat them as multibacillary if they have two or more peripheral nerve trunks involvement.

CLASSIFICATION BASED ON NUMBER OF SKIN LESIONS

One of the major concerns related to classification of leprosy is the over simplified approach for the field staff. Due to unavailability or unreliability of skin smears in many programs, purely clinical methods of classifying patients have been developed. According to the WHO Global Strategy for further reducing the leprosy burden and sustaining leprosy control activities (2006 – 2010), patients with 6 or more patches are classified as MB, whereas those with up to 5 patches as PB.[16] This classification was proposed to make classification simpler and to maintain reasonable balance between sensitivity and specificity. It must be recognized that this system will lead to a small but significant number of smear positive MB cases being treated with a PB treatment regimen and hence the increased risk of relapse in this small group of MB patients. In a study of 77 patients with 1 to 5 skin lesions, skin smears were positive in one patient, acid-fast bacilli (AFB) were found in 14 out of 77 skin biopsies and 4 patients had features of borderline lepromatous (BL) disease.[17] The significance of finding features of multibacillary disease on histopathology in patients grouped as PB leprosy remains unresolved and so is the drug regimen. Another important issue is that in the evolving disease even single lesion could be of multibacillary disease and even smear positive.[18] Also a larger number of PB patients will be over treated with MB regimen. Another issue in classification is need for a tool for differentiating between post MDT reactions and relapses which have similar clinical presentation and serious implications.

SLIT SKIN SMEARS

Skin smears have traditionally represented one of the cardinal signs of leprosy with specificity of 100%. However the sensitivity of this examination alone is low, because smear positive patients represent 10-50% of all patients as reported in various studies.[2] Moreover smears with few or scanty bacilli are likely to be missed. A degree of expertise is required in collecting material, staining and examining the slides for AFB.[15] Fear of transmission of HIV and hepatitis virus infections remains.

SKIN BIOPSY

A significant proportion of clinically obvious patients yield negative or doubtful histopathologic pictures and in practice most studies employ a combination of clinical and histopathologic criteria. Though specificity of histopathology is high, it may be difficult to distinguish relapse from reaction in treated PB patients[19] or to differentiate them from other granulomatous diseases like sarcoidosis, tuberculosis etc., some of which may be non-infective (foreign body granuloma). The biopsy if classical is of tremendous help, but in many situations a non-specific picture of chronic inflammation requires further help to arrive at a definitive diagnosis.

SEROLOGY AND MOLECULAR DIAGNOSTIC METHODS

The significance of anti PGL-I antibodies as a diagnostic serological test has been widely studied in the diagnosis of leprosy. The disadvantage of this assay is its lack of sensitivity especially in PB leprosy.[20] Other limitations of this test are its inability in diagnosing the early cases and its predicting value in identifying who will develop the disease in future.[21,22] Tests based on polymerase chain reaction (PCR) are potentially highly sensitive and specific, but since they require a sophisticated laboratory set up, they are not currently applicable in resource poor countries except as a research tool.[23,24] Recently, (ND)-O-bovine serum antigen (ND-O-BSA) based ELISA was found to be useful in screening of early infection with M. leprae and predicting / monitoring relapse.[25] However, funds and lack of infrastructure limits their application in most leprosy endemic countries of the world.

CORTICOSTEROID REGIMEN IN LEPRO Reaction (REVERSAL REACTION)

Corticosteroids remain the drug of choice in the treatment of reversal reactions (RRs). According to World Health Organization (WHO), the recommended dose is 40-60 mg daily which is gradually reduced
weeklly or fortnightly and stopped in 12 weeks duration[1]. The main effect of corticosteroids is to suppress the T-cell driven inflammatory response to M.leprae antigens within the skin and nerves. Therefore, the immunosuppressive doses of corticosteroids are required for prolonged periods, as the reaction will persist or recur even whilst the bacillary load gradually falls.[26] Rose and Waters[27] Naafs[28,29] have recommended that most BT patients require prednisolone for 4-9 months, BB patients for 6-9 months and BL patients for 6-18 months or even 24 months. Twelve weeks of prednisolone therapy for RRs in BB/BL patients has been found to be inadequate, with one-third of patients relapsing: however, extension of therapy to 20 weeks resulted in a low recurrence rate.[30] The existing reports provide conflicting data regarding adequate duration of steroid treatment in RRs.

TREATMENT OF NERVE FUNCTION IMPAIRMENT (NFI)

Damage to the nerve due to influx of inflammatory cells and their mediators is generally responsible for acute NFI.[31] Demyelination occurring as a sequel to atrophic changes in the axonal component and physiologic damage due to persistence of mycobacterial antigens in the Schwann cells or axons is responsible for more diffuse, insidious and gradually progressive NFI.[32] Within what period after the onset of nerve damage should corticosteroid therapy begin and how long to continue remains unanswered? WHO states that neuritis of less than 6 months duration should be treated with the standard 12 weeks regimen of oral prednisolone.[1] Patients with recent NFI of less than 6 months duration, demonstrate greater improvement in nerve function than those with old impairments.[30,33] However, van Brakel and Khawas[34] did note significant improvement in sensory function after 3 months prednisolone therapy in some patients with NFI of 6 months duration. It may be argued that NFI treated ‘early’ should respond better to treatment than when treated ‘late’, but very little evidence for this could be found in the literature.[35] More studies are needed to define the group of responsive patients, adequate length and dosage of corticosteroids more accurately. Leprosy reactions and new NFI occurred in a third of the study group (TRIPOD 3), emphasizing the need to keep patients under regular surveillance during MDT, and, where possible, after completion of MDT.[36]

CONCLUSIONS

Delayed and missed diagnosis of infectious patients of leprosy and lack of readily available tests to measure asymptomatic M. leprae infection in contacts continue to be deterring factors in disease control. The ideal diagnostic test/method should be simple, should identify all cases (100% sensitivity) and should be negative in people who do not have leprosy (100% specificity). Combining individual tests may improve the precision of a diagnostic procedure. According to published data, any single cardinal sign is inadequate as a diagnostic test. Almost 30% of all cases, including many MB patients, may not have detectable sensory loss to fine touch. Nerve involvement is not given any weightage in classification of the disease. Health workers are not trained to palpate and identify thickened peripheral nerve trunks in patients who may not have anaesthetic patches. The skin-smear and histopathology are not available in many settings and are not stressed upon even when facilities exist. The biggest problem in the management of leprosy is the nerve damage which occurs along the course of the disease per se, becomes acute during reactions and this results in deformities and disabilities. There is no parameter which can reliably predict what will be the likely nerve damage in a given patient and what dose of steroids, for what duration and instituted when, will give the best results. More studies may provide the answers. There should be no complacency in efforts to improve the diagnostic skills of health workers in identifying leprosy patients, development of better laboratory tools for early diagnosis of disease, to evaluate response to treatment and identifying patients at high risk of manifesting lepra reactions and nerve damage.

REFERENCES

5. Groenew G, Salha NG, Rashid MA, Hamid MA, Pattyn SR. Classification of leprosy cases under field conditions in Bangladesh: II, Reliability of clinical criteria. Lepr Rev