Leprosy type I reactions and erythema nodosum leprosum

Article *in* Anais Brasileiros de Dermatologia · February 2008

DOI: 10.1590/S0365-05962008000100010

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Leprosy type 1 reactions and erythema nodosum leprosum *

Reações hansênicas do tipo 1 e eritema nodoso hansênico *

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Abstract: Leprosy reactions are a major cause of nerve damage and morbidity in a significant proportion of leprosy patients. Reactions are immunologically mediated and can occur even after successful completion of multi-drug therapy. This review focuses on the epidemiology, pathology and treatment of leprosy type 1 reactions, erythema nodosum leprosum and silent neuropathy.
Keywords: Erythema nodosum; Leprosy; Leprosy/complications; Leprosy/therapy; Neuritis; Peripheral nervous system diseases

Resumo: *As reações hansênicas são a principal causa de dano e morbidade neural em grande parte dos pacientes hansênicos. São imunomediadas e podem ocorrer mesmo após o término bem sucedido da poliquimioterapia. Esta revisão enfoca a epidemiologia, a patologia e o tratamento das reações hansênicas do tipo 1, do eritema nodoso hansênico e da neuropatia silenciosa.*
Palavras-chave: Doenças do sistema nervoso periférico; Eritema nodoso; Hanseníase; Hanseníase/complicações; Hanseníase/terapia; Neurite

INTRODUCTION

Leprosy reactions are immunological phenomena that occur before, during or after the completion of multi-drug therapy (MDT). They contribute immensely to the burden of leprosy and need to be diagnosed and treated early to prevent nerve function impairment and permanent disability.

Dermatologists have an increasingly important role to play in the management of leprosy with the integration of leprosy services into general medical services worldwide.

Two major complications of leprosy are type 1 reactions (T1R) and erythema nodosum leprosum (ENL). These distinct conditions occur separately but may arise at different times in the same patient.[1,2] It is important to recognise that both these conditions can result in permanent loss of nerve function. Nerve function impairment (NFI) is defined as any reduction in sensory or motor function. Neuritis (inflammation of the peripheral nerve trunks) may or may not be accompanied by clinically detectable NFI.

TYPE 1 (REVERSAL) REACTIONS

A T1R is characterised by the development of acute inflammation in skin lesions or nerves or both.[3] Borderline leprosy is a strong risk factor for the occurrence of T1Rs [4] but individuals with polar forms of leprosy may also experience T1Rs. The onset of a T1R may be very rapid. T1Rs are frequently recurrent and this can lead to further nerve damage. [5]

Skin lesions become acutely inflamed and oedematous and may ulcerate. Oedema of the hands, feet and face can also be a feature of a reaction but systemic symptoms are unusual.

Acute neuritis leads to NFI which if not treated rapidly and adequately leads to permanent loss of nerve function causing peripheral sensory and/or motor neuropathy.

Skin lesions develop scaling in the chronic phase of T1R and may then mimic psoriasis, dermatophyte infections and cutaneous T-cell lymphoma.[6]

T1Rs may rarely occur many years after

Approved by the Editorial Board and accepted for publication on December 28, 2007.
* Work done at Department of Infectious and Tropical Diseases; London School of Hygiene and Tropical Medicine – London, United Kingdom.
Conflict of interest/Conflito de interesse: DNJ Lockwood was a paid adviser to Pharmion in 2003 during their application to the European Medicines Agency to have thalidomide licensed for the use in the treatment of ENL.
Financial funding/Suporte financeiro: None.

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completion of MDT. In this situation it may be difficult to distinguish between a late T1R and relapse.[7]

Epidemiology

The measured prevalence rates of T1R vary depending on whether the studies are conducted in hospital or field settings. Twenty-six per cent of Brazilian patients in Rio de Janeiro who had positive slit-skin smears experienced a T1R during the two year period they were taking MDT.[8] A retrospective study of individuals with borderline leprosy attending a leprosy referral centre in Nepal showed that 30% developed a T1R.[5] Half of the individuals who experienced a T1R had demonstrable new nerve function impairment.

A cohort of multibacillary (MB) patients recruited at two referral centres in north India had a prevalence rate of T1R of 19.8% at the time of first presentation.[9] A prospective hospital based study from Vietnam found a 29.1% prevalence of T1Rs. [10]

Risk factors

Extensive disease and having a positive slit skin smear are risk factors for T1Rs.[10,11] The detection of *Mycobacterium leprae* DNA by PCR in skin patches at the time of diagnosis is associated with an increased risk of T1R in Brazilian patients with a single skin lesion.[12] Increasing age has also been reported to be a risk factor for T1R in Vietnamese and Brazilians.[10,12] Individuals who present with WHO disability grades type 1 and 2 are significantly more likely to have severe T1Rs at diagnosis. [13] T1Rs are frequently seen after starting MDT or during the puerperium.[14]

Pathology of type 1 reactions

T1Rs are delayed hypersensitivity reactions.[15] The dermatopathological features of acute T1R are oedema, increased number of lymphocytes in the dermis and loss of normal granuloma organisation. As time passes there is an increase in the number of Langhans' giant cells.[15] A recent study of four histopathologists examining skin biopsies independently found that oedema and giant cells are the most sensitive indicators of T1R (personal communication).

M. leprae antigens have been demonstrated in the nerves and skin of patients experiencing T1Rs, localised to Schwann cells and macrophages.[16]

Schwann cells have been shown to express Toll-like receptor 2.[17] *M. leprae* infection may lead to the expression of MHC II on the surface of the cells. This may give rise to antigen presentation which triggers CD4 lymphocyte killing of the infected cell which is mediated by cytokines such as tumour necrosis factor (TNF).[18] Immunohistochemistry studies show greater TNF staining in the skin and nerves during T1Rs compared with non-reactional controls. [19] T1Rs appear to be mediated via Th1 lymphocytes and cells from reactional lesions express the pro-inflammatory cytokines interferon gamma (IFN-γ), interleukin 12 (IL-12) and the oxygen free radical producer inducible nitric oxide synthase.[20]

Treatment of type 1 reactions

Patients should be educated about T1Rs when being commenced on MDT. They should be advised to seek help immediately if they experience any of the symptoms and signs of a T1R.

The treatment of T1Rs is aimed at controlling the acute inflammation, easing pain and reversing nerve damage. MDT should be initiated in those presenting with a T1R or continued in those who develop a reaction whilst on it.

Individuals with inflamed skin lesions, neuritis or nerve function impairment are treated with oral corticosteroids. It is our practise to treat adults with 30-40mg of prednisolone daily for one month and gradually reduce the dose by 5mg per month. At each clinic visit it is essential to assess nerve function as accurately as possible. We use Semmes-Weinstein monofilaments (which are readily available in Brazil) and voluntary motor testing to ensure that nerve function is not deteriorating.

The current WHO Global Strategy document recommends treatment of severe T1Rs with "…a course of steroids, usually lasting 3-6 months".[21] Despite prolonged oral prednisolone only 60% will show improvement in nerve function.[22] The erythema and oedema of skin lesions will readily respond.

The recent Cochrane systematic review of "Corticosteroids for treating nerve damage in leprosy" identified only three randomised controlled trials(RCT) that met the review criteria.[23] Its conclusion was that evidence was lacking and that further RCTs are needed to identify the best treatment regimens.

A randomised controlled study comparing different steroid regimes suggested that duration rather than dose of treatment with prednisolone may be more important in controlling T1Rs.[24] In this study individuals who received prednisolone 30 or 60 mg tapered to zero over 20 weeks required less additional prednisolone than those randomised to receive prednisolone 60mg tapered over 12 weeks. Individuals with and without nerve involvement were enrolled into the study. A limitation of the study is that the primary outcome measures were failure to respond to treatment and physician determined requirement for additional prednisolone rather than improvement in nerve function or skin signs.

Treatment with a four month course of steroids

has been used to try and prevent reactional episodes, neuritis and nerve function impairment. The prednisolone had a protective effect whilst patients were taking it but at 12 months follow up this effect had been lost.[25]

The treatment of patients with steroids is not beneficial if their NFI has been present for longer than six months. The TRIPOD 3 study compared prednisolone with placebo and did not demonstrate any significant difference in improvement of nerve function between the two groups.[26]

In the rare instances where it is difficult to know whether a patient is suffering from a late reaction or relapse then a therapeutic trial of corticosteroids is recommended.[21]

Azathioprine in combination with a short course of prednisolone was as effective as a 12-week course of prednisolone in the management of T1Rs in Nepal.[27] Ciclosporin has been used in pilot studies in Nepal, Ethiopia and Brazil with some success.[28,29]

SILENT NEUROPATHY

Van Brakel and Khawas proposed the term "silent neuropathy" (SN) to describe the phenomenon of nerve function impairment occurring in the absence of symptoms. It is therefore only detected if physicians perform a careful examination of the peripheral nervous system. In Nepal 13% of patients developed SN. The majority of SN was present at diagnosis or developed during the first year of MDT.[30]

The treatment of SN is the same as for T1R. The duration of SN can not be ascertained from the history and we have a low threshold for giving a course of oral prednisolone.

ERYTHEMA NODOSUM LEPROSUM

ENL or type 2 reaction is a serious, difficult to manage immunological complication of borderline lepromatous (BL) and lepromatous leprosy (LL). The majority of patients with ENL go on to develop several episodes over many years, as multiple acute episodes or chronic ENL. [11,31] Less than 10% of patients in a large cohort in India had only a single episode of ENL while 62.5% had chronic ENL. [31]

The cutaneous manifestation of ENL is widespread crops of erythematous, inflamed nodules and papules, which may be superficial or deep.[3] Ulcerated, necrotic, pustular and bullous forms have also been reported. Some nodules may persist as a chronic painful panniculitis leading to fibrosis and scarring.[3]

Neuritis, in the form of painful enlarged nerves and nerve function impairment, may occur as part of ENL. The neuritis may be less dramatic than in T1R but it is important to recognise nerve involvement early to prevent permanent loss of function.

ENL may present as a systemic illness, with high fever, systemic upset and prostration. Peripheral oedema and transient proteinuria can also occur. Iritis and episcleritis can occur and may be sight threatening. Other features such as pain, photophobia and lacrimation may be absent.[3] Orchitis, lymphadenopathy, organomegaly, joint involvement, dactylitis and bone tenderness, especially over the tibia, are well recognised features of ENL.

Differential diagnosis

ENL should be considered in the differential diagnosis of erythema nodosum and other forms of panniculitis. ENL lesions differ from erythema nodosum by their evanescent nature and the large number of lesions involving sites other than the lower legs. ENL may also mimic Sweet's syndrome and septicaemia.[6]

Bullous ENL can be considered in the differential diagnosis of immunobullous disorders. Ulcerated lesions should be differentiated from pyoderma gangrenosum. Chronic ENL may also mimic connective tissue disorders or lymphoreticular malignancies.

A slit skin smear is a useful investigation which will rapidly confirm the presence of acid fast bacilli in the skin in ENL.[6]

Epidemiology and risk factors

There is wide geographic variation in the prevalence of ENL reactions. In Brazil 37% of new BL and LL cases experience ENL.[8] In Asia reported figures vary between 19-26% of BL and LL cases in Nepal, India and Thailand.[8,13,31,32]

ENL reactions occur most commonly during the first year of MDT. [31-33] One third of patients with ENL have the diagnosis of leprosy made at the same time as their reaction.[32,33]

Lepromatous leprosy (LL) and a bacillary index (BI) greater than 4+ have been shown to be risk factors for ENL.[31,32] Pregnancy, lactation, puberty, intercurrent infection, vaccination and psychological stress have been considered to precipitate ENL[3] but these associations have not been confirmed in prospective studies.

Pathology of erythema nodosum leprosum

The inflammatory infiltrate in ENL is situated in the dermis and the subcutis. The constituent cells vary with the timing of the skin biopsy. In acute lesions where skin biopsy is performed within 72 hours of occurrence, the predominant cell type is the neutrophil. Eosinophils and mast cells may also be present.[34] Skin biopsies performed later show fewer neutrophils and increasing numbers of lymphocytes, plasma cells and histiocytes, representing a chronic inflammatory infiltrate.

The other histological features reported in ENL

are oedema of the dermis and subcutis, vasculitis and panniculitis.[34] Changes due to leprosy will also be evident. The infiltrate due to LL may contain histiocytes with fatty change and foamy cells arranged diffusely. In biopsies from patients with BL leprosy the granuloma may contain histiocytes and lymphocytes.[35] In both cases large numbers of acid fast bacilli, usually granular in appearance, will be found.

Immune complexes are important in the pathogenesis of ENL as demonstrated by the presence of complexes of complement and *M. leprae* antigen in cutaneous lesions.[36,37] High levels of circulating TNF have been found in some individuals with ENL.[38] There is evidence of a cell mediated immune response in the pathogenesis of ENL. The major T cell subtype in ENL is the CD4+ cell in contrast to lepromatous leprosy where CD8+ cells predominate.[39,40] TNF and IL-6 have been shown to be present in skin lesions of ENL while IL-4 is absent or low [41-43] which supports a role for Th1 type T cells.

Treatment of erythema nodosum leprosum

The main aims in the management of ENL are the control of inflammation, pain relief and prevention of further episodes.[44] Mild cases of ENL can be treated with non steroidal anti-inflammatory drugs (NSAIDs).

- **Corticosteroids**

Prednisolone is commonly used for the management of moderate to severe ENL. The WHO Global Strategy document does not give specific advice concerning the dosage of prednisolone.[21] We commonly start at a dose of prednisolone 40-60mg daily but some leprologists use higher initial doses. The dose of prednisolone should be slowly reduced according to response. The majority of patients require multiple or prolonged courses of prednisolone due to the natural history of the condition.[31] Tachyphylaxis to prednisolone may also develop.

- **Concerns about the use of corticosteroids in the management of reactions**

The use of potent immunosuppressants is potentially problematic in areas endemic for severe infections such as tuberculosis. Immunosuppression may also lead to fatal strongyloidiasis.[45]

Analysis of the adverse events attributable to prednisolone in the three TRIPOD trials suggests that the drug is safe when used under field conditions in standardised regimes.[46] The trials used a total prednisolone dose of 1.96g and 2.52g. The steroid treated group were significantly more likely to experience minor adverse events but there was no difference in the likelihood of major adverse events between the prednisolone and placebo groups. Three hundred of the 815 patients enrolled in the three studies were followed for 24 months and none developed tuberculosis or hypertension during that time.

The long term adverse effects of corticosteroid therapy in individuals with leprosy reactions have not been studied. The amount of diabetes, cataract and hypertension experienced by this group is not known.

It has been reported that patients receiving steroids for ENL develop more adverse effects compared to those with T1Rs which may be due to the longer duration of treatment in this group.[47]

- **Thalidomide**

Thalidomide is very effective in the treatment of moderate to severe ENL. It has a rapid onset of action. Its beneficial effect is thought to be due to its action on TNF but other mechanisms may also play a part.[48] Prospective clinical trials have shown that treatment with thalidomide has a quicker action of onset and reduces the number of skin lesions, fever and systemic symptoms better than pentoxifylline, aspirin and placebo. [49-52] Treatment with thalidomide has also been shown to reduce the prednisolone requirement of patients with chronic ENL.[53]

We suggest using a starting dose of 400mg thalidomide at night in severe ENL and to reduce the dose to 300mg as soon as possible. This dose can then be reduced by 100mg per month but a maintenance dose may be required in those with chronic disease.[54]

Thalidomide should be used with extreme caution due to its teratogenic potential. The System for Thalidomide Education and Prescribing Safety (STEPS) programme adopted by the FDA in the USA has been shown to be very effective in preventing pregnancies in women taking thalidomide.[55] There has been a recent report of three cases of thalidomide embryopathy in Brazil and importantly tablet sharing was a major contributory factor.[56]

Women of child bearing potential who require thalidomide should be provided with information about its adverse effects and counselled on the importance of the need to avoid pregnancy. A negative pregnancy test should be obtained before starting thalidomide therapy and two methods of contraception should be prescribed. The pregnancy test should be repeated every month. Only one month's supply of thalidomide should be prescribed.[54] In many leprosy endemic countries such stringent arrangements are not possible.

Somnolence and dizziness are the commonest adverse affects of thalidomide. Cutaneous adverse effects occur in 3% of individuals[57] and may be exanthems or rarely erythema multiforme and toxic epidermal necrolysis.[58] Thalidomide causes a peripheral neuropathy but there are no data regarding thalidomide-induced

neuropathy in patients with ENL. Deterioration of nerve function in patients receiving thalidomide should not be assumed to be due to their leprosy.

- **Clofazimine**

Clofazimine is a mild anti-inflammatory agent. It can be used for the treatment of mild to moderate ENL but has a slow onset of action.[59] The clofazimine component of MB MDT probably reduces the incidence of ENL but this has not been formally tested.[60] Clofazimine at a dose of up to 300mg daily can be given to help control ENL. It is complicated by increased pigmentation and the possibility of clofazimine crystal enteropathy.[61,62] This higher dose should not be continued for more than 12 months.

- **Other drugs**

A recent Brazilian double blind RCT has shown that pentoxifylline is inferior to thalidomide in controlling cutaneous and systemic features of ENL. The pentoxifylline was also less well tolerated.[49] Colchicine and chloroquine have been evaluated in small studies and their effect was marginal. There are case reports and case series on the use azathioprine,[63] methotrexate,[64] oral zinc,[65] and the chimeric anti-TNF monoclonal antibody, infliximab,[66] for the treatment of ENL.

HIV AND LEPROSY REACTIONS

There is limited evidence from Uganda that T1Rs may occur more frequently in individuals with HIV and *M. leprae* co-infection[67] but this effect has not been replicated by studies from India or Mali although different methodologies were employed.[68,69]

T1Rs presenting as immune reconstitution disease in HIV positive individuals commenced on anti-retroviral therapy (ART) have been reported.[70,71]

There is no evidence to guide physicians in the optimal use of immunosuppression to manage T1Rs affecting HIV positive individuals. The current treatment of T1Rs in co-infected individuals is with corticosteroids as it is in HIV negative patients. The reported cases of T1Rs in co-infected individuals, whether ART related or not, have all been treated with corticosteroids. One individual required the introduction of azathioprine to control repeated relapses of his steroid dependent T1R.[72]

The adverse effect of additional immunosuppression in HIV positive patients with T1Rs is an obvious concern but there is no evidence to inform decisions about dose and duration of treatment in this group.

There are no good data on the effect of HIV infection on the frequency or clinical presentation of ENL in co-infected patients.

QUALITY OF LIFE, DISABILITY AND SOCIOECONOMIC IMPACT OF LEPROSY REACTIONS

The impact of leprosy reactions on quality of life and socioeconomic factors has not been formally assessed. The majority of work looking at disability due to leprosy has studied NFI in the context of MDT and not specifically reactions. It is widely accepted that reactions are important in the causation of disability.

Ocular complications due to reactions can lead to blindness. The presence of potentially blinding leprosy-related eye disease is associated with "reaction involving the face."[73]

CONCLUSION

The management of leprosy reactions and silent neuropathy continues to be a major challenge. The prompt diagnosis and effective treatment of these complications of leprosy are essential if nerve function impairment, deformity and disability are to be minimised. ❑

Acknowledgements

Dr Kahawita is supported by a Training Fellowship from the Ministry of Health, Sri Lanka. Dr Walker is supported by grants from LEPRA, the American Leprosy Mission, the Special Trustees of the Hospital for Tropical Diseases, London and the Geoffrey Dowling Fellowship of the British Association of Dermatologists.

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How to cite this article / Como citar este artigo: Kahawita IP, Walker SL, Lockwood DNJ. Leprosy type 1 reactions and erythema nodosum leprosum. An Bras Dermatol. 2008;83(1):75-82.