ANTROPOLOGIA / SOCIAL / HISTÓRIA / ESTIGMA

Robertson J. The leprosy asylum in India: 1886-1947. J Hist Med Allied Sci. 2009 Oct; 64(4): 474-517.

Writing against a historical practice that situates the leprosy asylum exclusively within prison-like institutions, this article seeks to show the variation in leprosy asylums, the contingencies of their evolution, and the complexity of their designs, by devoting attention to the characteristics of the leprosy asylum in India from 1886 to 1947, in particular to the model agricultural colony. Drawing upon the travel narratives of Wellesley Bailey, the founder of the Mission to Lepers in India, for three separate periods in 1886, 1890-91, and 1895-96, it argues that leprosy asylums were formed in response to a complex conjunction of impulses: missionary, medical, and political. At the center of these endeavors was the provision of shelter for persons with leprosy that accorded with principles of good stewardship and took the form of judicious use of donations provided by benefactors. As the Mission to Lepers began to bring about improvements and restructuring to asylums, pleasant surroundings, shady trees, sound accommodation, and good ventilation became desirable conditions that would confer physical and psychological benefits on those living there. At the same time, the architecture of the asylum responded to economic imperatives, in addition to religious and medical aspirations, and asylums moved towards the regeneration of a labor force. Leprosy-affected people were increasingly employed in occupations that contributed to their sustenance and self-sufficiency, symbolically reincorporating the body damaged by leprosy into the economic world of productive relations.

Gusmão AP, Antunes MJ. To be with leprosy and to work as a nurse: histories of fight and overcoming. Rev Bras Enferm. 2009 Nov-Dec; 62(6): 820-4.

This research aimed at knowing the history of ex-workers, leprosy patients admitted compulsorily from the early twentieth century in Brazil. Leprosy, fraught with prejudice and stigma in the early 20s was treated for decades with stringent policies of compulsory isolation of patients in hospitals colonies. Because of prejudice, there was difficulty in hiring staff to maintain these establishments. The stories of the individuals came from taped interviews with seven residents of the colony, by the method of oral history. The research results partially presented in this paper reported the life histories of individuals, their struggles, sorrows and dreams. It was confirmed that the patients themselves were keepers of services within the colonies, including nursing.

Hirai Y. Review of the time "Kaishun Byoshitsu" was founded: is the date "1899" correct? Nippon Ishigaku Zasshi. 2009 Dec; 55(4): 427-43

It has been an accepted story until today that in 1899 Kensuke Mitsuda's efforts led to the founding of "Kaishun Byoshitsu", an isolation ward for leprosy patients in Japanese modern times first located in the Tokyo City Yoikuin (poorhouse). But, in this paper, the author has collected as many documents that describe the details of the foundation of "Kaishun Byoshitsu" as possible, and thoroughly further reexamined definite sources regarding the time when it was founded. The documents are classified into the following four by the author, [A]: Kensuke Mitsuda himself, [B]: the persons concerned with Mitsuda, [C]: the persons involved in Yoikuin, and [D]: general researchers. These classifications [A] to [D], are further divided into two insistences, according to whether the founding date was claimed to be in 1899 or in 1901 in [D]. Insistences are exhibited in [B] for "in 1899" and in [C] for "in 1901", respectively. However, there was no conclusive "definite source" clearly specified in the above-mentioned classifications [A] to [D]. Additionally, in the most reliable classification [A], there is no actual reference to the founding date. Therefore, the author has reached the conclusion that at least the claim that the founding date was 1899, though it has become an accepted story, is not based on any solid evidence

Boldsen JL. Leprosy in Medieval Denmark--osteological and epidemiological analyses. Anthropol Anz. 2009 Dec; 67(4): 407-25.

A total of 3033 skeletons from 11 medieval Danish cemeteries and 99 skeletons from the North Scandinavian me-

dieval site of Westerhus were examined for seven lesions indicative of leprosy. The seven lesions are: rounding to the edge of the nasal aperture, degeneration of spina nasalis anterior, degeneration of the alveolar process of the pre-maxilla, porosity or perforation of the palatine process of maxilla, sub-periostal exostoses on the fibula, general swelling of the shaft of the fibula, and degeneration of the 5th metatarsal bone. The dichotomous scores of these lesions were used to estimate sensitivity and specificity of the lesion scores in relation to leprosy and to estimate sample point prevalence of leprosy at death among adults. In turn the estimates of sensitivity and specificity were used to calculate an individual comprehensive statistic, lamda, indicating leprosy status. Among adults the lamda statistic did not associate with age at death, but this cannot be taken as a sign of lack of selective mortality for leprosy but a combination of the opposing effects of long waiting time before developing leprosy related lesions and short survival with these lesions. In urban communities sufferers of leprosy were institutionalized when the leprosarium was established (in Odense around 1275); in rural communities this did not happen but the pattern of burial does indicate an internal segregation of sufferers. In the early Middle Ages (AD 1150-1350) the point prevalence at death among adults of leprosy was higher in rural (25-40 percent) than in urban (10-20 percent) communities, and villages close to town showed lower frequencies of leprosy than villages situated further away from these centers. Leprosy declined in the late Middle Ages, first in towns and cities, later in rural communities. In Odense and Malmö it appears that leprosy was effectively eliminated by 1350 whereas there were still sufferers of leprosy at Øm Kloster around 1550. Leprosy appears to have been less common in North Scandinavia than in South Scandinavia, and there are some indications that leprosy was much more common in the Sámi population than in the North population of North Scandinavia. It is suggested that the rapid and early decline of leprosy in the towns was caused by the breaking of chains of infection by institutionalizing the most affected sufferers from leprosy. In rural communities it is suggested that the later decline of leprosy was brought about by a natural vaccination with the active substance in the Calmette vaccine, Mycobacterium bovis.

BIOLOGIA MOLECULAR

Yap VB, Lindsay H, Easteal S, Huttley G. Estimates of the effect of natural selection on protein-coding content. Mol Biol Evol. 2010 Mar; 27(3): 726-34.

Analysis of natural selection is key to understanding many core biological processes, including the emergence of competition, cooperation, and complexity, and has important applications in the targeted development of vaccines. Selection is hard to observe directly but can be inferred from molecular sequence variation. For protein-coding nucleotide sequences, the ratio of nonsynonymous to synonymous substitutions (omega) distinguishes neutrally evolving sequences (omega = 1) from those subjected to purifying (omega < 1) or positive Darwinian (omega > 1) selection. We show that current models used to estimate omega are substantially biased by naturally occurring sequence compositions. We present a novel model that weights substitutions by conditional nucleotide frequencies and which escapes these artifacts. Applying it to the genomes of pathogens causing malaria, leprosy, tuberculosis, and Lyme disease gave significant discrepancies in estimates with approximately 10-30% of genes affected. Our work has substantial implications for how vaccine targets are chosen and for studying the molecular basis of adaptive evolution.

BIOQUÍMICA

Murase T, Zheng RB, Joe M, Bai Y, Marcus SL, Lowary TL, et al. Structural insights into antibody recognition of mycobacterial polysaccharides. J Mol Biol. 2009 Sep 18; 392(2): 381-92.

Mycobacteria are major human pathogens responsible for such serious and widespread diseases as tuberculosis and leprosy. Among the evolutionary adaptations essential for pathogenicity in mycobacteria is a complex carbohydrate-rich cell-wall structure that contains as a major immunomodulatory molecule the polysaccharide lipoarabinomannan (LAM). We report here crystal structures of three fragments from the non-reducing termini of LAM in complex with a murine antibody Fab fragment (CS-35Fab). These structures reveal for the first time the

three-dimensional structures of key components of LAM and the molecular basis of LAM recognition at between 1.8- and 2.0-A resolution. The antigen-binding site of CS-35Fab forms three binding pockets that show a high degree of complementarity to the reducing end, the branch point and one of the non-reducing ends of the Y-shaped hexasaccharide moiety found at most of the non-reducing termini of LAM. Structures of CS-35Fab bound to two additional tetrasaccharides confirm the general mode of binding seen in the hexasaccharide and indicate how different parts of LAM are recognized. Altogether, these structures provide a rational basis for understanding the overall architecture of LAM and identify the key elements of an epitope that may be exploited for the development of novel and more effective antimycobacterial vaccines. Moreover, this study represents the first high-resolution X-ray crystallographic investigation of oligofuranoside-protein recognition.

Nakao H, Matsunaga I, Morita D, Aboshi T, Harada T, Nakagawa Y, et al. Mycolyltransferase from Mycobacterium leprae excludes mycolate-containing glycolipid substrates. J Biochem. 2009 Nov; 146(5): 659-65.

Trehalose dimycolate (TDM) is a major surface-exposed mycolyl glycolipid that contributes to the hydrophobic cell wall architecture of mycobacteria. Nevertheless, because of its potent adjuvant functions, pathogenic mycobacteria appear to have evolved an evasive maneuver to down-regulate TDM expression within the host. We have shown previously that Mycobacterium tuberculosis (M.tb) and Mycobacterium avium (M.av), replace TDM with glucose monomycolate (GMM) by borrowing host-derived glucose as an alternative substrate for the FbpA mycolyltransferase. Mycobacterium leprae (M.le), the causative microorganism of human leprosy, is also known to down-regulate TDM expression in infected tissues, but the function of its mycolyltransferases has been poorly analysed. We found that, unlike M.tb and M.av FbpA enzymes, M.av FbpA was unexpectedly inefficient in transferring alpha-branched mycolates, resulting in impaired production of both TDM and GMM. Molecular modelling and mutational analysis indicated that a bulky side chain of leucine at position 130 of M.le FbpA obstructed the intramolecular tunnel that was proposed to accommodate the alpha-branch portion of the substrates. Notably, even after a highly reductive evolution, M.le FbpA remained functional in terms of transferring unbranched acyl chains, suggesting a role that is distinct from that as a mycolyltransferase.

CIRURGIA / REABILITAÇÃO / INCAPACIDADES

Redondo A. Peripheral nerve surgery in leprosy. Neurochirurgie. 2009 Oct; 55(4-5): 421-6.

Leprosy has nearly disappeared in France but continues to affect two million patients in the world. Involvement of the peripheral nerve must be identified and requires surgical treatment, which can provide good results for pain and function. The author reviews the most frequently affected peripheral nerves and reports her personal series, with surgery performed concomitantly with the medical treatment of the disease.

Jin Y, Tan Y, Wang J, Zhong H, Yue J, Li H, et al. Effect of different surgical methods on leprosy plantar ulcers. Zhongguo Xiu Fu Chong Jian Wai Ke Za Zhi. 2009 Oct; 23(10):1183-6.

OBJECTIVE: To explore the effects of different surgical methods on plantar ulcers in leprosy. METHODS: The clinical data of 71 patients with leprosy plantar ulcers and treated with different surgical methods between October 1950 and October 2006 were analyzed retrospectively. In group A, 34 cases underwent debridement, including 26 males and 8 females aged 53-88 years old (average 72.4 years old); the course of ulcer averaged 29.0 years; the size of ulcer ranged from 5 cm x 3 cm x 2 cm to 11 cm x 7 cm x 3 cm; the disability degrees of the affected foot was mild in 25 cases and severe in 9 cases according to the self-designed evaluation system. In group B, 22 cases received foot pressure rebuilding surgery, including 19 males and 3 females aged 48-83 years old (average 69.8 years old); the course of ulcer averaged 33.5 years; the size of ulcer ranged from 5 cm x 3 cm x 2 cm to 12 cm x 7 cm x 3 cm; the disability degrees of the affected foot was mild in 12 cases and severe in 10 cases. In group

C, 15 cases were repaired with the transposition of toe flap, foot arch flap, acrotarsium flap, or medial tibia flap, including 11 males and 4 females aged 43-73 years old (average 64.6 years old); the course of ulcer averaged 29.3 years; the size of ulcer ranged from 6 cm x 3 cm x 2 cm to 11 cm x 5 cm x 3 cm; the disability degrees of the affected foot was mild in 9 cases and severe in 6 cases. No significant differences were evident among three groups in terms of the general information ($P > 0.05$), except for the difference between group A and group C on age ($P < 0.05$). RESULTS: Group A: 19 out of 34 cases healed and the average healing time was 46.8 days; all patients were followed up for 2-45 years (average 17.2 years); the rate of ulcer healing 1 year after operation was 55.9% (19/34); 12 healed ulcer patients relapsed at average 1.5 years after operation; the rate of ulcer healing at last follow-up was 20.6% (7/34). Group B: 18 out of 22 cases healed and the average healing time was 29.2 days; all patients were followed up for 2-50 years (average 13.3 years); the rate of ulcer healing 1 year after operation was 81.8% (18/22); 7 healed ulcer patients relapsed at average 3.3 years after operation; the rate of ulcer healing at last follow-up was 50.0% (11/22). Group C: 14 out of 15 cases healed and the average healing time was 27.1 days; all patients were followed up for 3-12 years (average 8.8 years). The rate of ulcer healing 1 year after operation was 93.3% (14/15); 7 healed ulcer patients relapsed at average 4 years after operation; the rate of ulcer healing at final follow-up was 46.7% (7/15). For the rate of ulcer healing 1 year after operation, there was a significant difference between group A and group B, and between group A and group C ($P < 0.05$), but no significant difference was evident between group B and group C ($P > 0.05$). For the rate of ulcer healing at the final follow-up visit, there was a significant difference between group A and group B ($P < 0.05$), but no significant difference was evident between group A and group C, and between group B and group C ($P > 0.05$). CONCLUSION: The surgical treatment of plantar ulcers in leprosy should include the alleviation of the plantar high-pressure zone and the transposition of the flaps, providing good short-term and long-term therapeutic effect.

CLÍNICA / INVESTIGAÇÃO CLÍNICA

Medeiros S, Coelho R, Fernandes C, Catarino MC, Afonso A, Vieira R, et al. Leprosy and Kaposi sarcoma presenting as an immune reconstitution inflammatory syndrome in a patient with AIDS. J Am Acad Dermatol. 2009 Sep; 61(3): 516-8.

The simultaneous presence of infectious organisms within cutaneous lesions of Kaposi sarcoma in persons with AIDS has been demonstrated. We describe a patient with concurrent leprosy and Kaposi sarcoma presenting as an immune reconstitution inflammatory syndrome in the setting of AIDS.

Rijal A, Rijal S, Bhandari S. Leprosy coinfection with kala-azar. Int J Dermatol. 2009 Jul; 48(7): 740-2.

Leprosy and visceral leishmanias are endemic in Nepal and are both major public health problems. Two patients of visceral leishmaniasis developed leprosy during the course of the disease. Leprosy and visceral leishmaniasis share a similar immunological spectrum and can occur concomitantly in endemic regions.

Vinay K, Smita J, Nikhil G, Neeta G. Human immunodeficiency virus and leprosy coinfection in Pune, India. J Clin Microbiol. 2009 Sep; 47(9): 2998-9.

We report eight cases and the incidence of leprosy in human immunodeficiency virus (HIV)-infected individuals after initiation of antiretroviral treatment (ART). The incidence of leprosy in patients on ART was 5.22 per 1,000 person-years (95% confidence interval, 2.25 to 10.28). This high incidence suggests that there should be regular examination of HIV-infected individuals for clinical signs of leprosy.

Guditi S, Ram R, Ismal KM, Sahay M, Dakshinamurthy KV, Girish N, et al. Leprosy in a renal transplant recipient: review of the literature. Transpl Infect Dis. 2009 Dec; 11(6): 557-62.

A 52-year-old male underwent living-related renal transplantation. He received prednisolone, azathioprine, and

cyclosporine as immunosuppression protocol. Eleven years after transplantation, he developed pyrexia with multiple nodular lesions on his limbs, trunk, and face. Skin biopsy and smears showed the presence of numerous acid-fast bacilli with 5% sulfuric acid indicative of Mycobacterium leprae. He was initiated on multidrug therapy (MDT) including dapsone, clofazimine, and rifampicin. After 2 years of MDT, he developed new multiple erythematous, tender subcutaneous nodules in crops over his face and upper limbs. Skin biopsies and histopathological examination confirmed the diagnosis of type 2 lepra reaction or erythema nodosa leprosum. He was managed with an increase in the dose of prednisolone and thalidomide. He was continued on MDT.

Choon SE, Tey KE. Lucio's phenomenon: a report of three cases seen in Johor, Malaysia. Int J Dermatol. 2009 Sep; 48(9): 984-8.

BACKGROUND: Lucio's phenomenon is a rare and aggressive necrotising variant of erythema nodosum leprosum that classically occur in patients with undiagnosed, diffuse non-nodular lepromatous leprosy. It is a potentially fatal leprosy reaction characterised by extensive, bizarrely-shaped, painful purpuric skin lesions and ulcerations. Lucio's phenomenon is very rarely reported outside of Mexico and Costa Rica. METHODS: We describe 3 cases seen in Johor, Malaysia. RESULTS: The first two cases responded to the prompt simultaneous institution of daily rifampicin, dapsone, clofazimine and prednisolone. Case 3 continued to have new lesions and extension of existing lesions while on dapsone and clofazimine. The subsequent addition of rifampicin and prednisolone prevented new lesion formation but patient succumbed to the extensive cutaneous infarcts and consequent sepsis. CONCLUSIONS: Early diagnosis and prompt institution of multi-drug therapy together with prednisolone may improve the prognosis and outcome of Lucio's phenomenon.

Reveiz L, Buendía JA, Téllez D. Chemoprophylaxis in contacts of patients with leprosy: systematic review and meta-analysis. Rev Panam Salud Publica. 2009 Oct; 26(4): 341-9.

To identify and summarize randomized clinical trials (RCTs) that assessed the effectiveness of chemoprophylaxis to prevent leprosy in contacts of patients newly diagnosed with the disease. METHODS: All studies were extracted from Medline (PubMed 1966 to November 2008), the Cochrane Controlled Trials Register (number 3 2008), LILACS (1982 to November 2008), and Scirus (November 2008). Manual searches and searches of crossed references of assessed articles were also done. RCTs' risk of bias was assessed according to the methodology proposed by the Cochrane Collaboration. The main outcome measure was diagnosis of leprosy (secondary cases) in contacts of patients with the disease (primary cases). RESULTS: The search identified 320 references, from which 7 RCTs with a total of 66 311 participants were included and evaluated. The combined results from the RCTs favored chemoprophylaxis to placebo with 2-4 years of follow-up (6 RCTs, 66 107 participants, relative risk (RR) 0.59, 95% confidence interval (CI) 0.50-0.70, I(2) = 0 (I(2) describes percent total variation across studies caused by heterogeneity)). Single-dose rifampicin (21 711 participants, RR 0.43, 95% CI 0.28-0.67, number needed to treat 285), dapsone once or twice weekly for at least 2 years (3 RCTs, 43 137 participants, RR 0.60, 95% CI 0.48-0.76, I(2) = 0), and acedapsone every 10 weeks for 7 months (2 RCTs, 1 259 participants, RR 0.49, 95% CI 0.33-0.72, I(2) = 0) were significantly superior to placebo in preventing secondary cases of leprosy. CONCLUSION: Chemoprophylaxis is effective in lowering the incidence of leprosy in contacts of patients diagnosed with the disease.

Rada E, Aranzazu N, Convit J. Immune response of Hansen's disease. Invest Clin. 2009 Dec; 50(4): 513-27

Hansen's disease presents a wide spectrum of clinical and histopathological manifestations that reflect the nature of the immunological response of the host towards diverse Mycobacterium leprae components.

The immunological system, composed by both innate and adaptive immunology, offers protection towards infections of various etiologies, among them bacterial. Bacteria, of course, have developed multiple strategies for evading host defenses, based on either very complex or simple mechanisms, but with a single purpose: to "resist" host attacks and to be able to survive. We have tried to summarize some recent studies in Hansen's disease, with more emphasis in the inmunology area. We think that in the future, all illnesses should also be very strongly related to other important aspects such as the social, environmental and economic, and whose development is not solved in a laboratory.

Sheetal S, Arvind C. Lest we forget Hansen's disease (leprosy): an unusual presentation with an acute onset of inflammatory polyarthritis and the rheumatology experience. Int J Rheum Dis. 2009 Apr; 12(1): 64-9.

Several forms of arthritis and rheumatism can sometimes complicate leprosy. However, its presentation as an acute onset arthritis is unusual. We report two adult male naïve patients who presented to our rheumatology outpatient clinic with acute onset inflammatory polyarthritis, skin rash and mild sensory neurodeficit. Borderline lepromatous leprosy (in type I lepra reaction) was diagnosed. We also refer to 19 case records of Hansen arthritis in the clinic database (1998-2007) from approximately 35,000 patients and a community study to highlight the missed diagnosis of Hansen's disease and its unusual association with rheumatoid arthritis. In countries like India where leprosy is endemic, this disease also merits attention in rheumatology clinics.

DIAGNÓSTICO

Rongioletti F, Gallo R, Cozzani E, Parodi A. Leprosy: a diagnostic trap for dermatopathologists in nonendemic area. Am J Dermatopathol. 2009 Aug; 31(6):607-10.

Leprosy is a chronic infectious disease caused by Mycobacterium leprae, presenting with different clinicopathological forms. These great variety of presentations make the diagnosis of leprosy a difficult challenge in countries where the disease is not endemic. Moreover, a discordance between the clinical and histopathological diagnosis in classifying a case of leprosy can complicate the issue. We report a 43-year-old woman in whom the diagnosis of leprosy was challenging, especially, because the biopsy was sent without any clinical suspicion and Italy is a nonendemic area. The clinical informations described simply an annular lesion, and histopathology disclosed a superficial and deep moderate perivascular and periadnexal infiltrate in the dermis, predominantly made of lymphocytes with some histiocytes, in the absence of granuloma formation, foamy histiocytes, or giant cells. Only the clinicopathological correlation based upon the patient's family history, her Brazilian origin, and her anesthetic lesions led us to the suspicion of leprosy. We reviewed the slides with more serial cuts and with special stains that eventually revealed a slight perineural lymphohistiocytic infiltrate and the presence of rare bacilli in the nerves, more consistent with indeterminate leprosy. However, the clinical features and the detection of just few bacilli in the skin lesions and skin smears were more consistent with a borderline leprosy. The discordance between the clinical and histopathological diagnosis in the setting of leprosy is discussed.

Kulkarni M, Chauhan V, Bharucha M, Deshmukh M, Chhabra A. MRI imaging of ulnar leprosy abscess. J Assoc Physicians India. 2009 Feb; 57: 175-6.

Leprosy is a chronic granulomatous infection, caused by mycobacterium leprae, primarily affecting the peripheral nerve trunks and cutaneous nerves. It classically presents with neural or dermal signs and symptoms. The indolent course of leprosy may manifest as erythema nodosum (appearance of tender inflamed subcutaneous nodule) and reversal reaction (inflammation in the previous skin lesion, appearance of new skin lesions, neuritis and abscess). Ulnar nerve is most commonly involved. This report illustrates the MR imaging appearance of ulnar nerve abscess.

Neonakis IK, Gitti Z, Kontos F, Baritaki S, Zerva L, Krambovitis E, et al. Report of 2 indigenous cases of leprosy from a European country: use of polymerase chain reaction-restriction fragment length polymorphism analysis of hsp65 gene for identification of Mycobacterium leprae directly from a clinical sample. Diagn Microbiol Infect Dis. 2009 Jul; 64(3): 331-3.

In this article, we report on 2 indigenous cases of leprosy detected in a European country. We also report on the use of polymerase chain reaction-restriction fragment length polymorphism analysis of hsp65 gene for rapid identification of Mycobacterium leprae directly from the clinical sample.

Slim FJ, Illarramendi X, Maas M, Sampaio EP, Nery JA. The potential role of magnetic resonance imaging in patients with Hansen's neuropathy of the feet: a preliminary communication. Int J Low Extrem Wounds. 2009 Sep; 8(3): 169-73.

A magnetic resonance imaging (MRI) protocol was performed in leprosy patients with a neuropathic foot and superficial ulcers and/or localized cellulitis but no clinical suspicion of osteomyelitis. The aim of the study was to determine if unsuspected osteomyelitis was present in this defined group of leprosy patients. A total of 15 neuropathic feet from 9 patients were included. Clinically and on MRI, the forefoot was predominantly affected. MRI findings of osteomyelitis were found in 4 feet. In feet with osteomyelitis, 3 had a superficial ulcer and 3 had clinical signs of localized cellulitis. A clinical diagnosis of cellulitis was confirmed on MRI in 2 feet.A striking discrepancy between clinical and MRI findings was found.This study shows that, compared with clinical evaluation, MRI is a sensitive method for the detection of unsuspected osteomyelitis in neuropathic feet with superficial ulcers and/or cellulitis. MRI findings in this group of patients may influence clinical decision making and may prevent further complications, because osteomyelitis requires more aggressive medical treatment. This preliminary communication should pave the wave for designed controlled studies so that patients with Hansen's neuropathy may get the best medical care.

Elias JJ, Nogueira-Barbosa MH, Feltrin LT, Furini RB, Foss NT, Marques W J, et al. Role of ulnar nerve sonography in leprosy neuropathy with electrophysiologic correlation. J Ultrasound Med. 2009 Sep; 28(9): 1201-9.

OBJECTIVE: The purpose of this study was to evaluate the diagnostic usefulness of ulnar nerve sonography in leprosy neuropathy with electrophysiologic correlation. METHODS: Twenty-one consecutive patients with leprosy (12 men and 9 women; mean age +/- SD, 47.7 +/- 17.2 years) and 20 control participants (14 men and 6 women; mean age, 46.5 +/- 16.2 years) were evaluated with sonography. Leprosy diagnosis was established on the basis of clinical, bacteriologic, and histopathologic criteria. The reference standard for ulnar neuropathy in this study was clinical symptoms in patients with proven leprosy. The sonographic cross-sectional areas (CSAs) of the ulnar nerve in 3 different regions were obtained. Statistical analyses included Student t tests and receiver operating characteristic curve analysis. RESULTS: The CSAs of the ulnar nerve were significantly larger in the leprosy group than the control group for all regions ($P < .01$). Sonographic abnormalities in leprosy nerves included focal thickening (90.5%), hypoechoic areas (81%), loss of the fascicular pattern (33.3%), and focal hyperechoic areas (4.7%). Receiver operating characteristic curve analysis showed that a maximum CSA cutoff value of 9.8 mm(2) was the best discriminator (sensitivity, 0.91; specificity, 0.90). Three patients with normal electrophysiologic findings had abnormal sonographic findings. Two patients had normal sonographic findings, of which 1 had abnormal electrophysiologic findings, and the other refused electrophysiologic testing. CONCLUSIONS: Sonography and electrophysiology were complementary for identifying ulnar nerve neuropathy in patients with leprosy, with clinical symptoms as the reference standard. This reinforces the role of sonography in the investigation of leprosy ulnar neuropathy.

Salekzamani Y, Shakouri SK, Houshyar Y, Ghanjeyfar V, Samarbakhsh A, Shamaizadeh M, et al. Clinical, electrodiagnostic and pedobarographic assessments of leprotic patients with trans-tibial amputation. Pak J Biol Sci. 2009 Aug 15; 12(16): 1134-9.

The aim of present study was to investigate clinical, electrodiagnostic and pedobarographic findings of non-amputee limb in chronic leprotic patients with unilateral trans-tibial amputation to determine neuropathy and plantar foot pressure in non-amputee limb. During the present prospective cross-sectional study, 10 chronic leprotic patients with unilateral trans-tibial amputation were evaluated. The study was conducted in Tabriz Babaghi and Imam Reza Hospitals at summer of 2008. Sensory nerve conduction (SNAP) and Compound Motor Action Potentials (CMAP) studies were performed in association with pedobarographic assessment. No reliable response was detected from tested sensory and motor nerves, except a very low amplitude finding in deep preoneal nerve of one patient. In comparing with healthy group, static total plantar area, dynamic total plantar area, static rarefoot peak pressure and dynamic rarefoot peak pressure were lower in leprotic patients ($p = 0.047$, $p = 0.004$, $p = 0.029$ and $p < 0.001$), while static forefoot peak pressure and dynamic forefoot peak pressure were higher in these patients ($p = 0.011$ and $p = 0.031$). All of leprotic patients with unilateral trans-tibial amputation suffered from severe neuropathy. Also, these patients have high plantar pressure under the forefoot. Collectively, severe neuropathy and abnormal plantar foot pressure expose in non-amputee foot expose leprotic patients to the higher risk of secondary amputation

Slim FJ, Faber WR, Maas M. The role of radiology in nerve function impairment and its musculoskeletal complications in leprosy. Lepr Rev. 2009 Dec; 80(4): 373-87.

Conventional techniques, such as plain radiography and bone-scintigraphy, were used in the past to evaluate skeletal changes in patients with leprosy. More recent publications focus on radiological imaging of affected nerves, and involve advanced modalities such as Computed Tomography (CT-scan), Ultrasonography (US), and Magnetic Resonance Imaging (MRI). US and MRI can play an especially important role in the evaluation of nerve involvement in newly diagnosed patients, and also during leprosy reactions. This is important, because when nerve involvement is diagnosed in time, it may be reversible with adequate treatment. Radiological modalities can also play an important role during the followup of patients with leprosy with nerve function impairment. Skeletal and soft-tissue abnormalities occur, even after treatment. The so-called neuropathic foot is a well known consequence. Because of nerve function impairment, there is a constant risk of developing ulcers and subsequent osteomyelitis, or neuro-osteoarthropathy (Charcot foot or tarsal disintegration), which can lead to the amputation of the affected limb. Different radiological modalities can be used during the evaluation and follow-up of patients with leprosy with a neuropathic foot. With this up-to-date review, we highlight the importance and potential role of radiological imaging techniques in leprosy.

Liu D, Li G, Huang W, Gao J, Yue C, Xiao Q. Analysis of newly detected leprosy cases and misdiagnosis in Wuhan (1990-2004). Lepr Rev. 2009 Dec; 80(4):410-5.

To analyse the leprosy epidemiological trends and the diagnostic delay in newly detected cases between 1990 and 2004 in Wuhan. METHODS: We reviewed the clinical records of all 80 leprosy patients who were referred to the Wuhan Institute of Dermatology and Venerology (WHIDV) during 1990 and 2004, and the clinical information of diagnosis-delayed cases was analysed. RESULTS: Patients were determined as lepromatous leprosy (LL, 24, 30%), borderline lepromatous leprosy (BL, 15, 18-75%), borderline leprosy (BB, 9, 11.25%), borderline tuberculoid leprosy (BT, 12, 15%), and tuberculoid leprosy (TT, 20, 25%), respectively. The patients were more likely to present with multibacillary (MB, 48 cases) rather than with paucibacillary (PB, 32 cases). Among the 80 newly detected patients, 53 cases (66.25%) had been misdiagnosed (51 cases in general hospitals, two cases in WHIDV), 23 cases were treated with hospitalisation in department of dermatology of general hospitals. Up to

20 kinds of dermatological conditions involved in case misdiagnosis. CONCLUSIONS: Misdiagnosis of dermatological conditions and ignorance of the disease among general practitioners and hospital dermatologists were the main causes of diagnostic delay in Wuhan. which is leading to incorrect treatment for patients suffering with a variety of damage due to leprosy.

Lopez MG, Dias DS. Diagnóstico tardío de Lepra: presentación de un caso. Mediciego oct. 2009; 15(supl.2).

La lepra es una enfermedad granulomatosa de evolución crónica, infecciosa, poco contagiosa, producida por el Micobacterium Leprae, que se caracteriza por lesiones cutáneas y de los nervios periféricos; además puede afectar otras estructuras, como mucosas de las vías respiratorias, ojos, músculos, hígado, testículos, etc. La Lepra Lepromatosa es la forma maligna de la enfermedad. Su diagnóstico tardío hace que el paciente presente discapacidades irreversibles. Presentamos un caso de una paciente con Lepra, de 8 años de evolución, con una discapacidad grado II, que le imposibilita una buena calidad de vida.

EDUCAÇÃO

Kanthraj GR. Classification and design of teledermatology practice: what dermatoses? Which technology to apply?. J Eur Acad Dermatol Venereol. 2009 Aug; 23(8): 865-75.

Dermatologists are mostly confined to urban regions and rural population is deprived of specialist care. Teledermatology Practice (TDP) is a solution to overcome this global problem. Tools for TDP includes video conference, store and forward, hybrid, mobile, satellite communication, integration model, nurse-led teledermatology, teledermatology focusing on difficult-to-manage cases, teledermoscopy, and teledermatopathology with combined applications. This article reviews the feasibility studies focusing teledermatology tools and analyses the possible options in designing TDP. Categorizing dermatoses for TDP depends on the purpose and types of technology. The dermatoses presenting from a remote geographic regions requires any of the following approaches (i) only TDP, (b) initial TDP followed by face-to-face, (iii) initial face-to-face followed by TDP and (iv) only face-to-face examination. The technology should suit the dermatoses, meet the purpose, be cost-effective and provide better management with follow-up care. We recommend store and forward as a basic TDP model as most dermatoses are diagnosed and follow-up care is delivered. Leprosy, pigmented skin lesions, leg ulcers, HIV and endemic dermatoses require screening and triage services using mobile teledermatology. Counselling and education require videoconference. Rural dermatology's camps require satellite communication mounted on a vehicle. Objective assessment (vitiligo and leg ulcer) after treatment requires integration model at a tertiary centre. Difficult-to-manage cases require second opinion using hybrid/store and forward TDP. Lower rural centre are provided with mobile/ store and forward teledermatology services. Selected or major community centre should be equipped with hybrid teledermatology and linked to a tertiary centre. This process helps healthcare administration to plan a TDP to cover all dermatoses, utilizing the available health care professional (HCP) and technology with minimum budget investment.

Paixão MP, Miot HA, Wen CL. Tele-education on leprosy: evaluation of an educational strategy. Telemed J E Health. 2009 Jul-Aug; 15(6): 552-9.

The purpose of this research was to evaluate educational strategies applied to a tele-education leprosy course. The curriculum was for members of the Brazilian Family Health Team and was made available through the Sao Paulo Telehealth Portal. The course educational strategy was based on a constructivist learning model where interactivity was emphasized. Authors assessed motivational aspects of the course using the WebMAC Professional tool. Forty-eight healthcare professionals answered the evaluation questionnaire. Adequate internal consistency was achieved (Cronbach's alpha = 0.79). More than 95% of queried items received good evaluations. Multidimensional analysis according to motivational groups of questions (STIMULATING, MEANINGFUL, ORGANIZED,

EASY-TO-USE) showed high agreement. According to WebMAC's criteria, it was considered an "awesome course." The tele-educational strategies implemented for leprosy disclosed high motivational scores.

John AS, Rao PS. Awareness and attitudes towards leprosy in urban slums of Kolkata, India. Indian J Lepr. 2009 Jul-Sep; 81(3): 135-40.

Urban slums have proliferated in India with poor health and socio-economic status with no organized health system. They are at high risk for contracting communicable diseases including leprosy. In order to obtain reliable data on knowledge, attitudes and treatment of leprosy; a random sample cluster survey was done in Kolkata slums. House to house screening for leprosy was done in 6 representative random samples of slums, each with a population of at least 5000, using accepted methods for detection. Suspects were confirmed by medical officers. Intensive interviews were done by qualified male and female investigators. A majority had some knowledge of leprosy but hardly any knew early signs or symptoms or where to get proper diagnosis and treatment. Half the respondents felt leprosy must be treated separately from general patients but stated they had no hesitation in working with or visiting a leprosy patient. There were 11 suspects of which 9 were confirmed for leprosy and sent to nearest centre for MDT. Glaring gaps are noticed between knowledge and practice of slum population regarding leprosy. An integrated health program is needed urgently in urban slums to control leprosy and other diseases using a variety of resources including medical colleges

ENFERMAGEM / PREVENÇÃO

Gusmao APB, Antunes MJM. Ter hanseníase e trabalhar na enfermagem: história de lutas e superação. Rev. bras. Enferm nov.-dez. 2009; 62(6):820-4.

A pesquisa teve como objetivo conhecer a história dos ex-trabalhadores de enfermagem, que tiveram hanseníase internados compulsoriamente desde início do século XX no Brasil. A hanseníase, permeada de preconceitos e estigmas, no início dos anos 20 foi tratada por décadas com severas políticas públicas de isolamento compulsório dos doentes em Hospitais Colônias. Devido ao preconceito, havia dificuldade em contratar recursos humanos para manter estes estabelecimentos. As histórias dos sujeitos pesquisados surgiram a partir de entrevistas gravadas com sete moradores da colônia, pelo método da história oral. Os resultados da pesquisa apresentados parcialmente neste trabalho relatam as histórias de vida dos sujeitos, suas lutas, sofrimentos e sonhos. Confirmou-se que os próprios doentes eram mantenedores dos serviços dentro das colônias, inclusive os de Enfermagem.

EPIDEMIOLOGIA / DETECÇÂO / CONTROLE / PREVALÊNCIA / ELIMINAÇÃO

Sakamuri RM, Kimura M, Li W, Kim HC, Lee H, Kiran MD, et al. Population-based molecular epidemiology of leprosy in Cebu, Philippines. J Clin Microbiol. 2009 Sep; 47(9): 2844-54.

To address the persisting problem of leprosy in Cebu, Philippines, we compiled a database of more than 200 patients who attend an established referral skin clinic. We described the patient characteristics in conventional demographic parameters and also applied multiple-locus variable-number tandem-repeat (VNTR) analysis (MLVA) and single nucleotide polymorphism (SNP) typing for Mycobacterium leprae in biopsied skin lesion samples. These combined approaches revealed that transmission is ongoing, with the affected including the young Cebuano population under 40 years of age in both crowded cities and rural areas of the island. The emergence of multicase families (MCF) is indicative of infection unconstrained by standard care measures. For the SNPs, we designed a low-cost PCR-restriction fragment length polymorphism typing method. MLVA in M. leprae was highly discriminatory in this population yet could retain broad groups, as defined by the more stable SNPs, implying temporal marker stability suitable for interpreting population structures and evolution. The majority of isolates belong to an Asian lineage (SNP type 1), and the rest belong to a putative postcolonial lineage (SNP type 3). Specific alleles at two VNTR loci, (GGT)5

and 21-3, were highly associated with SNP type 3 in this population. MLVA identified M. leprae genotype associations for patients with known epidemiological links such as in MCFs and in some villages. These methods provide a molecular database and a rational framework for targeted approaches to search and confirm leprosy transmission in various scenarios.

Couppié P, Domergue V, Clyti E, Guedj M, Vaz T, Sainte-Marie D, et al. Increased incidence of leprosy following HAART initiation: a manifestation of the immune reconstitution disease. AIDS. 2009 Jul 31; 23(12): 1599-600.

A retrospective cohort study was conducted to determine whether the incidence of leprosy varied with the duration of antiretroviral therapy (ART). Between 1992 and 2006, seven cases of leprosy were observed. The incidence of leprosy in untreated patients was 0.7 per 1000 person-years, 13 per 1000 person-years in persons receiving HAART for more than 3 months and 0.9 per 1000 person-years for persons receiving HAART for more than 3 months. The adjusted hazard ratio was 18.5 (95% confidence interval, 1.6-217) with P = 0.02. In tropical areas where HAART is increasingly available, physicians should be aware of the possibility of incident leprosy shortly after HAART initiation.

Guimarães HC, Barros AL, Bassoli SR, Salotti SR, Oda RM, Lunney M. Helping a man with leprosy: a case study. Int J Nurs Terminol Classif. 2009 Jul-Sep;20(3): 141-4.

PURPOSE: This case study illustrates nursing diagnoses and interventions for a man with leprosy. DATA SOURCES: Data sources were published literature on the disease of leprosy, and the experience and expertise of the authors in working with people with leprosy. DATA SYNTHESIS: Data were synthesized using the standardized nursing languages of North American Nursing Diagnosis Association International and the Nursing Interventions Classification. The accuracy of the diagnoses and the appropriateness of the nursing interventions were supported by the positive health outcomes of the patient. CONCLUSIONS: Although leprosy has been eradicated in some countries, the risk of new cases is present anywhere that Mycobacterium leprae still exists. The recommended treatment of multibacilar polychemotherapy has lowered the rate of new cases in Brazil. IMPLICATIONS FOR NURSING PRACTICE: Nurses need to incorporate evidence-based practice interventions for leprosy-based wound care, and nurses should encourage persons with leprosy to maintain regular medical care with multibacilar polychemotherapy.

Nsagha DS, Bamgboye EA, Oyediran AB. Operational barriers to the implementation of multidrug therapy and leprosy elimination in Cameroon. Indian J Dermatol Venereol Leprol. 2009 Sep-Oct; 75(5): 469-75.

BACKGROUND: The World Health Organization targeted to eliminate leprosy from the world with multidrug therapy (MDT) by 2000. But, leprosy remains a problem in Essimbiland of Menchum Division of Cameroon, with a prevalence of 1.7/10,000 and high rate of case detection in children. AIMS: To assess knowledge and practices on the cure of leprosy, treatment duration, drug availability and problems faced by leprosy patients acquiring drugs in order to enhance MDT implementation and leprosy elimination in Menchum and Boyo divisions. METHODS: Observational study in which a structured questionnaire was administered to leprosy patients, their contacts and a control group. RESULTS: 480 respondents were interviewed and 405 (84.8%) (95% confidence interval [CI]: 81.6-87.2%) knew that leprosy can be cured. These respondents comprised 166 (92.2%) of 180 contacts, 129 (93.5%) of 138 patients and 110 (67.9%) of 162 controls. Two hundred and fourteen (44.6%) (95% CI: 40.1-48.9%) respondents knew that leprosy treatment is free, comprising of 110 (51.4%) patients, 99 (46.3%) contacts and five (2.3%) controls. A statistically significant difference in the knowledge on free treatment of leprosy was found to exist between leprosy patients, contacts and controls, with leprosy patients having a better knowledge (79.71%) (95% CI: 73-86.42%), followed by contacts (55.0%) (95% CI: 47.73-62.26%) and controls (3.1%) (95% CI: 0.43-5.77%) (P = 0.00). Pertinent problems faced by patients in get-

ting MDT included distant health facilities and poor road network (91[19.0%]), lack of confidence in treatment (56 [11.7%]), MDT shortage (45 [9.4%]), few health facilities (52 [10.8%]), gratification demands (25 [5.2%]), disturbance from other illnesses (24 [5.0]), ignorance (21 [4.4%]) and poor relationship with nurses (24 [5.0%]). CONCLUSION: Patients still face problems in getting free MDT. Better MDT implementation and leprosy elimination strategies are proposed.

Moriyama K, Kikuch I, Ishii N. [Children born to Hansen's disease patients in Amami-Oshima, Kagoshima, Japan. Nihon Hansenbyo Gakkai Zasshi. 2009 Sep; 78(3): 231-50.

In the Japanese leprosaria, it was very difficult or almost impossible for leprosy patients to give birth to their children. There were various reasons for this situation. Leprosy in the women mostly worsened in pregnancy and some of the children developed leprosy. Because of the chronic nature of the disease, marriage was encouraged in Japanese leprosaria, so that vasectomy was usually enforced in men who were wed, while artificial abortion was enforced in pregnant women. The only one exception was the situation of the Amami Wako-en Leprosarium. The Wako-en Leprosarium was started in 1943, and between 1946 and 1953, it was under American rule. Later it was transferred to Japanese rule. Religions such as Buddhism, Christianity and other religions greatly helped with leprosy patients, and in the Wakoen, it was Catholicism which prevailed. Catholic believer Joan Matsubara (later the secretary of Wako-en), Father Patrick Finn, Kaoru Ohira (director) outlined how children born to Hansen's disease patients would be grown up and made the internal rules of the couples' dormitory, while this was impossible in other leprosaria. Between 1953 and 1954, children were brought up by Matsubara's family or nurses. And since November 1954, children were brought up at nurseries (firstly named "Children's House" and later at "Naze Engel House" and children between 2 and 3 years went to "White Lily House". The children could meet their parents at times and now they are full-fledged grown-up citizens.

Gain M, Ghnaya H, Lepeytre F, Toledano C, Cabane J, Tiev KP. Leprosy: a rare imported disease. Rev Med Interne. 2009 Dec; 30(12): 1064-6.

Although rare in occidental countries, leprosy is an endemic disease throughout the world. Physicians may encounter imported cases and thus need to be aware of this diagnosis. We here report a 41-year-old male patient from French West Indies who presented with nonspecific extensive skin lesions and a peripheral neuropathy. Skin biopsy examination led to the diagnosis of borderline lepromatous leprosy.

Cardona-Castro N, Beltrán-Alzate JC, Romero-Montoya M. Clinical, bacteriological and immunological follow-up of household contacts of leprosy patients from a post-elimination area - Antioquia, Colombia. Mem Inst Oswaldo Cruz. 2009 Sep; 104(6): 935-6.

Follow-up of the household contacts (HHC) of leprosy patients is still the best strategy for early detection of leprosy. HHC from a post-elimination region of Colombia studied in 2001-2002 were re-contacted in 2007. They were tested at both times by clinical examination, bacillary index (BI), PCR from a slit skin smear (SSS) and anti PGL-1 IgM titres. Thirty-two of 61 HHC (52%) were re-contacted. Nine HHC (28%) showed sero-conversion and one had a skin lesion (BI negative, nested PCR positive). Periodic evaluation of HHC can contribute to the detection of infected HHC as well as new and early leprosy cases.

Srisungnam S, Rudeeaneksin J, Lukebua A, Wattanapokayakit S, Pasadorn S, Mahotarn K, et al. Molecular epidemiology of leprosy based on VNTR typing in Thailand. Lepr Rev. 2009 Sep; 80(3): 280-9.

Recently about 500 new cases of leprosy have been reported each year in Thailand. In addition to a steady rate of new case detection, Thailand is in Southeast Asia where leprosy is endemic in neighbouring countries; therefore, strain differentiation could be useful in tracing origins and routes of infection, and general leprosy surveillance. To identify suitable markers for differentia-

tion of M. leprae strains in different global geographic regions and to determine the applicability of a systematic genotyping method for tracing leprosy transmission, variable nucleotide tandem repeats (VNTRs) of 14 loci were evaluated using DNA extracts from a total of 97 skin biopsies and slit skin smear samples. The alleles per locus ranged from 2-26 providing adequate strain differentiation. Microsatellite loci (GAA)21, (AT)17 are highly polymorphic followed by (GTA)9, (AC)8a, (AC)8b, and (AC)9. The minisatellites 6-7, 21-3 and 27-5 exhibited a limited number of alleles. The repeat of 23-3 showed no polymorphism. Overall, the strain types can be divided into two distinct Thai groups, according to the alleles at the (GGT)5 and 21-3 loci. However, there are no obvious geographical patterns of distribution of VNTR strain types. Closely matched VNTR profiles found in household members of two multi-case families suggested infection through a common source.

Penna ML, de Oliveira ML, Penna GO. The epidemiological behaviour of leprosy in Brazil. Lepr Rev. 2009 Sep; 80(3): 332-44.

BACKGROUND: The elimination strategy reduced known leprosy prevalence but the detection rate remains high in many countries, including Brazil. The high Brazilian detection rate imposes a limit to the reduction of known prevalence in the short term. The knowledge of time behaviour and spatial distribution of leprosy statistics will contribute to decision making for leprosy control. METHOD: The numbers of newly diagnosed leprosy cases by region and year from 1980 to 2004, and prevalent cases from 1990 to 2007 were fitted as a parabolic function of time in negative binomial regression models. To detect areas with increased leprosy detection rates we used spatial scan statistics for cases detected from 2005 to 2007 in the three regions where leprosy is still a public health problem. RESULTS: All detection rate series except the one for the south region showed statistically significant regression coefficients for time and time squared, showing an initial increasing trend. Scan statistics detected 29 statistically significant spatial clusters. These clusters cover 789 municipalities with a total of 51,904 cases detected. CONCLUSION: Time behaviour of the detection rate is probably a result of better access to primary health care. According to spatial scan statistics, Brazil can be divided into highly endemic areas, containing 11.2% of the total Brazilian population, with a mean detection rate in 2007 of 76.4 per 100,000 inhabitants, and areas of much lower endemicity, containing 888% of the population with a mean detection rate of 132. Leprosy is concentrated in a small proportion of the Brazilian population.

Siddiqui MR, Velidi NR, Pati S, Rath N, Kanungo AK, Bhanjadeo AK, et al. Integration of leprosy elimination into primary health care in orissa, India. PLoS One. 2009 Dec 18;4(12): e8351.

Leprosy was eliminated as a public health problem (<1 case per 10,000) in India by December 2005. With this target in sight the need for a separate vertical programme was diminished. The second phase of the National Leprosy Eradication Programme was therefore initiated: decentralisation of the vertical programme, integration of leprosy services into the primary health care (PHC) system and development of a surveillance system to monitor programme performance. METHODOLOGY/ PRINCIPAL FINDINGS: To study the process of integration a qualitative analysis of issues and perceptions of patients and providers, and a review of leprosy records and registers to evaluate programme performance was carried out in the state of Orissa, India. Program performance indicators such as a low mean defaulter rate of 3.83% and a low-misdiagnosis rate of 4.45% demonstrated no detrimental effect of integration on program success. PHC staff were generally found to be highly knowledgeable of diagnosis and management of leprosy cases due to frequent training and a support network of leprosy experts. However in urban hospitals district-level leprosy experts had assumed leprosy activities. The aim was to aid busy PHC staff but it also compromised their leprosy knowledge and management capacity. Inadequate monitoring of a policy of 'new case validation,' in which MDT was not initiated until primary diagnosis had been verified by a leprosy expert, may have led to approximately 26% of suspect cases awaiting confirmation of diagnosis 1-8 months after their initial PHC visit. CONCLUSIONS/SIG-

NIFICANCE: This study highlights the need for effective monitoring and evaluation of the integration process. Inadequate monitoring could lead to a reduction in early diagnosis, a delay in initiation of MDT and an increase in disability rates. This in turn could reverse some of the programme's achievements. These findings may help Andhra Pradesh and other states in India to improve their integration process and may also have implications for other disease elimination programmes such as polio and guinea worm (dracunculiasis) as they move closer to their elimination goals.

Mastrangelo G, Scoizzato L, Fadda E, Silva GV, Santos LJ, Cegolon L. Epidemiological pattern of leprosy in an endemic area of North-East Brazil, 1996-2005: the supporting role of a Nongovernmental Organization. Rev Soc Bras Med Trop. 2009 Dec; 42(6): 629-32.

In an endemic area of North-East Brazil (the town of Picos, State of Piauí), a nongovernmental organization (NGO) supported the activity against leprosy in connection with governmental health organizations and local agents. The indicators of leprosy elimination were compared over time (within Picos) and across space (Picos versus Piauí). The case detection rate, above 8 per 10,000 people in the last two years of observation, increased over time in Picos (p=0.010). This finding could be due to active detection activities rather than expanding endemicity, as suggested by the reduction in leprosy in children (p=0.053) and the decrease in the proportion of new cases with grade 2 disability (p<0.001). These indicators showed a more favorable time trend in the city than in the State, suggesting that NGO activity was supportive in the battle towards leprosy control.

Castro NC, Beltrán-Alzate JC, Romero-Montoya M. Clinical, bacteriological and immunological follow-up of household contacts of leprosy patients from a post-elimination area - Antioquia, Colombia. Mem. Inst. Oswaldo Cruz sept. 2009; 104(6): 935-6.

Follow-up of the household contacts (HHC) of leprosy patients is still the best strategy for early detection of leprosy. HHC from a post-elimination region of Colombia studied in 2001-2002 were re-contacted in 2007. They were tested at both times by clinical examination, bacillary index (BI), PCR from a slit skin smear (SSS) and anti PGL-1 IgM titres. Thirty-two of 61 HHC (52 percent) were re-contacted. Nine HHC (28 percent) showed seroconversion and one had a skin lesion (BI negative, nested PCR positive). Periodic evaluation of HHC can contribute to the detection of infected HHC as well as new and early leprosy cases.

Koba A, Ishii N, Mori S, Fine PE. The decline of leprosy in Japan: patterns and trends 1964-2008. Lepr Rev. 2009 Dec; 80(4): 432-40.

Our purpose was to elucidate the patterns and trends of autochthonous leprosy in Japan from 1964 to 2008, to compare them with the findings from other studies of leprosy in decline, and to determine whether M. leprae transmission persists in Japan. DESIGN: Data on registered leprosy cases in Japan in the period 1964-2008 were analysed with reference to trends in case detection, geographical distribution, age at diagnosis, sex, classification, family history and broad correlation with socioeconomic conditions. RESULTS: A consistent decline in leprosy case detection was observed in all areas of the country over the period 1964-2008. Highest incidence was consistently in Okinawa, the southernmost part of Japan. Autochthonous leprosy has not been reported in anyone born in Japan since 1980. Increasing average age and a shift towards lower latitudes were demonstrated throughout the period. There was an inverse association between regional measures of wealth and leprosy incidence. CONCLUSIONS: Leprosy has declined throughout the past century in Japan. Autochthonous transmission has probably stopped in mainland Japan, but may still occur at a low level in Okinawa, the country's southernmost region. Analyses of data on autochthonous cases revealed patterns similar to those reported in other countries with declining leprosy. Detailed comparisons between countries with very low leprosy incidence may help us to better understand the epidemiology of leprosy.

Imbiriba ENB, Silva Neto AL, Souza WV, Pedrosa V, Cunha MG, Garnelo L. Desigualdade social, crescimento urbano e hanseníase em Manaus: abordagem espacial. Rev. saúde pública ago. 2009; 43(4):656-65.

Analisar a epidemiologia de hanseníase segundo a distribuição espacial e condições de vida da população. MÉTODOS: Estudo ecológico baseado na espacialização da hanseníase em Manaus (AM), entre 1998 e 2004. Os 4.104 casos obtidos do Sistema de Informações de Agravos de Notificação foram georreferenciados de acordo com a localização dos endereços em 1.536 setores censitários urbanos, por meio de quatro técnicas: correios (73,7 por cento dos endereços encontrados); Programa de Cadastro de Logradouros (7,3 por cento); Programa Saúde da Família (2,1 por cento) e folhas de coleta do Instituto Brasileiro de Geografia e Estatística (1,5 por cento). Para cálculo do coeficiente de detecção utilizou a população de 2001. Na análise espacial foi aplicado o método bayesiano empírico local para produzir uma estimativa do risco da hanseníase, suavizando o efeito da flutuação das taxas, quando calculadas para pequenas áreas. Para análise da associação entre espacialização e fatores de risco empregou-se a regressão logística, tendo como variáveis explicativas a ocorrência de casos em menores de 15 anos (indicador de gravidade) e o Índice de Carência Social construído a partir das variáveis do Censo 2000. RESULTADOS: O coeficiente de detecção apresentou-se hiperendêmico em 34,0 por cento dos setores e muito alto em 26,7 por cento. A medida de associação (odds ratio) referente às variáveis explicativas foi significativa. A combinação de baixa condição de vida e ocorrência em menores de 15 anos foi adotada para identificar as áreas prioritárias para intervenção. CONCLUSÕES: A análise espacial da hanseníase mostrou que a distribuição da doença é heterogênea, atingindo mais intensamente as regiões habitadas por grupos em situação de maior vulnerabilidade.

Mastrangelo G, Scoizzato L, Fadda E, Silva GV, Santos LJ, Cegolon L. Epidemiological pattern of leprosy in an endemic area of North-East Brazil, 1996-2005: the supporting role of a Nongovernmental Organization. Rev. Soc. Bras. Med. Trop Dec. 2009; 42(6): 629-32.

In an endemic area of North-East Brazil (the town of Picos, State of Piauí), a nongovernmental organization (NGO) supported the activity against leprosy in connection with governmental health organizations and local agents. The indicators of leprosy elimination were compared over time (within Picos) and across space (Picos versus Piauí). The case detection rate, above 8 per 10,000 people in the last two years of observation, increased over time in Picos (p=0.010). This finding could be due to active detection activities rather than expanding endemicity, as suggested by the reduction in leprosy in children (p=0.053) and the decrease in the proportion of new cases with grade 2 disability (p<0.001). These indicators showed a more favorable time trend in the city than in the State, suggesting that NGO activity was supportive in the battle towards leprosy control.

Machado CM, Martins TC, Colturato I, Leite MS, Simione AJ, Souza MP, et al. Epidemiology of neglected tropical diseases in transplant recipients: review of the literature and experience of a Brazilian HSCT center. Rev. Inst. Med. Trop. São Paulo oct.-dec. 2009; 51(6):309-24.

The rising success rate of solid organ (SOT) and haematopoietic stem cell transplantation (HSCT) and modern immunosuppression make transplants the first therapeutic option for many diseases affecting a considerable number of people worldwide. Consequently, developing countries have also grown their transplant programs and have started to face the impact of neglected tropical diseases (NTDs) in transplant recipients. We reviewed the literature data on the epidemiology of NTDs with greatest disease burden, which have affected transplant recipients in developing countries or may represent a threat to transplant recipients living in other regions. Tuberculosis, Leprosy, Chagas disease, Malaria, Leishmaniasis, Dengue, Yellow fever and Measles are the topics included in this review. In addition, we

retrospectively revised the experience concerning the management of NTDs at the HSCT program of Amaral Carvalho Foundation, a public transplant program of the state of São Paulo, Brazil.

Oliveira TA, Lana FCF. Hanseníase no município de Ouro Preto, Minas Gerais: aspectos epidemiológicos e operacionais. REME jul.-set. 2009; 13(3): 407-15.

A hanseníase, doença infectocontagiosa causada pela Mycobacterium leprae, possui uma imagem social histórica, e o desenvolvimento da ciência não foi capaz de mudar a resposta de medo e preconceito da sociedade perante essa doença.Trata-se de um estudo descritivo do tipo transversal, cujo objetivo foi analisar a epidemiologia da hanseníase no município de Ouro Preto, no período de 2002 a 2008, visando formular estratégias para o controle da doença na região e identificar possíveis áreas homogêneas com riscos de transmissão. Foram coletados dados do Sistema de Informação de Agravos e Notificações (SINAN), no setor de Epidemiologia do município. Os resultados mostraram que todas as notificações foram realizadas na Policlínica Municipal de Ouro Preto. Há a existência de um possível cluster da doença no distrito de Santa Rita, uma vez que 72% das notificações eram de residentes desse distrito, o que sugere uma área remanescente de alta incidência da doença na antiga Vila Rica. A taxa de detecção média da hanseníase no município foi de 2,1/10 mil habitantese, em Santa Rita, de 24,5/10 mil, caracterizando a região como hiperendêmica. Observou-se, ainda, que os casos emmenores de 15 anos representaram 2,9% do total e que a taxa de detecção em 2002, 2006 e 2008 foi de 0,5/10 mil habitantes,demonstrando transmissão ativa da doença. Assim, constatou-se a necessidade de descentralizar os serviços de saúde afim de atingir melhorias no acesso e resolutividade, além da realização de novas pesquisas sobre a história e seus determinantes.

GENÉTICA

Nakamura K, Akama T, Bang PD, Sekimura S, Tanigawa K, Wu H, et al. Detection of RNA expression from pseudogenes and non-coding genomic regions of Mycobacterium leprae. Microb Pathog. 2009 Sep; 47(3): 183-7.

We have previously reported that some pseudogenes are expressed in Mycobacterium leprae (M. leprae), the causative agent of leprosy, and that their expression levels alter upon infection of macrophages. We attempted to further examine the expression of pseudogene and non-coding genomic region in M. leprae, in this study. 19 Pseudogenes, 17 non-coding genomic regions, and 21 coding genes expression in M. leprae maintained in the footpads of the hypertensive nude rat (SHR/NCrj-rnu) were examined by reverse transcriptase polymerase chain reaction (RT-PCR). The expression of some of these pseudogenes, non-coding genomic regions and coding genes were also examined in M. leprae from skin smear specimens obtained from patients with lepromatous leprosy by RT-PCR. Transcripts from pseudogenes, non-coding genomic regions and coding genes examined in this study were clearly observed in M. leprae. The expression patterns of some of these transcripts vary greatly among different leprosy patients. These results indicate that some of pseudogenes and non-coding genomic regions are transcribed in M. leprae and analysis of RNA expression patterns including pseudogene and non-coding genomic region in M. leprae may be useful in understanding the pathological states of infected patients.

Hamann L, Kumpf O, Schuring RP, Alpsoy E, Addo GB, Bienzle U, et al. Low frequency of the TIRAP S180L polymorphism in Africa, and its potential role in malaria, sepsis, and leprosy. BMC Med Genet. 2009 Jul 14;10: 65.

BACKGROUND: The Toll-like receptors (TLRs) mediate innate immunity to various pathogens. A mutation (S180L) in the TLR downstream signal transducer TIRAP has recently been reported to be common in Europeans and Africans and to roughly half the risks of heterogeneous

infectious diseases including malaria, tuberculosis, bacteremia, and invasive pneumococcal disease in heterozygous mutation carriers. METHODS: We assessed the TIRAP S180L variant by melting curve and RFLP analysis in 1095 delivering women from malaria-endemic Ghana, as well as in a further 1114 individuals participating in case control studies on sepsis and leprosy in Germany, Turkey and Bangladesh. RESULTS: In Ghana, the TIRAP S180L polymorphism was virtually absent. In contrast, the mutation was observed among 26.6%, 32.9% and 12% of German, Bangladesh and Turkish controls, respectively. No significant association of the heterozygous genotype with sepsis or leprosy was observed. Remarkably, homozygous TIRAP 180L tend to increase the risk of sepsis in the German study (P = 0.04). CONCLUSION: A broad protective effect of TIRAP S180L against infectious diseases per se is not discernible.

Singh P, Tripathi P, Silva GH, Pingoud A, Muniyappa K. Characterization of Mycobacterium leprae RecA intein, a LAGLIDADG homing endonuclease, reveals a unique mode of DNA binding, helical distortion, and cleavage compared with a canonical LAGLIDADG homing endonuclease. J Biol Chem. 2009 Sep 18; 284(38): 25912-28.

Mycobacterium leprae, which has undergone reductive evolution leaving behind a minimal set of essential genes, has retained intervening sequences in four of its genes implicating a vital role for them in the survival of the leprosy bacillus. A single in-frame intervening sequence has been found embedded within its recA gene. Comparison of the M. leprae recA intervening sequence with the known intervening sequences indicated that it has the consensus amino acid sequence necessary for being a LAGLIDADG-type homing endonuclease. In light of massive gene decay and function loss in the leprosy bacillus, we sought to investigate whether its recA intervening sequence encodes a catalytically active homing endonuclease. Here we show that the purified M. leprae RecA intein (PI-MleI) binds to cognate DNA and displays endonuclease activity in the presence of alternative divalent cations, Mg2+ or Mn2+. A combination of approaches, including four complementary footprinting assays such as DNase I, copper-phenanthroline, methylation protection, and KMnO4, enhancement of 2-aminopurine fluorescence, and mapping of the cleavage site revealed that PI-MleI binds to cognate DNA flanking its insertion site, induces helical distortion at the cleavage site, and generates two staggered double strand breaks. Taken together, these results implicate that PI-MleI possesses a modular structure with separate domains for DNA target recognition and cleavage, each with distinct sequence preferences. From a biological standpoint, it is tempting to speculate that our findings have implications for understanding the evolution of the LAGLIDADG family of homing endonucleases.

Han XY, Sizer KC, Thompson EJ, Kabanja J, Li J, Hu P, et al. Comparative sequence analysis of Mycobacterium leprae and the new leprosy-causing Mycobacterium lepromatosis. J Bacteriol. 2009 Oct; 191(19): 6067-74.

Mycobacterium lepromatosis is a newly discovered leprosy-causing organism. Preliminary phylogenetic analysis of its 16S rRNA gene and a few other gene segments revealed significant divergence from Mycobacterium leprae, a well-known cause of leprosy, that justifies the status of M. lepromatosis as a new species. In this study we analyzed the sequences of 20 genes and pseudogenes (22,814 nucleotides). Overall, the level of matching of these sequences with M. leprae sequences was 90.9%, which substantiated the species-level difference; the levels of matching for the 16S rRNA genes and 14 protein-encoding genes were 98.0% and 93.1%, respectively, but the level of matching for five pseudogenes was only 79.1%. Five conserved protein-encoding genes were selected to construct phylogenetic trees and to calculate the numbers of synonymous substitutions (dS values) and nonsynonymous substitutions (dN values) in the two species. Robust phylogenetic trees constructed using concatenated alignment of these genes placed M. lepromatosis and M. leprae in a tight cluster with long terminal branches, implying that the divergence occurred long ago. The dS and dN values were also much higher than those for other closest pairs of mycobacteria. The dS values were 14 to 28% of the dS values for M. leprae and Mycobacterium tuberculosis, a more divergent pair

of species. These results thus indicate that M. lepromatosis and M. leprae diverged approximately 10 million years ago. The M. lepromatosis pseudogenes analyzed that were also pseudogenes in M. leprae showed nearly neutral evolution, and their relative ages were similar to those of M. leprae pseudogenes, suggesting that they were pseudogenes before divergence. Taken together, the results described above indicate that M. lepromatosis and M. leprae diverged from a common ancestor after the massive gene inactivation event described previously for M. leprae.

Silva SA, Mazini PS, Reis PG, Sell AM, Tsuneto LT, Peixoto PR, et al. HLA-DR and HLA-DQ alleles in patients from the south of Brazil: markers for leprosy susceptibility and resistance. BMC Infect Dis. 2009 Aug 22; 9: 134.

BACKGROUND: Many epidemiological studies have shown that the genetic factors of the host play a role in the variability of clinical response to infection caused by M. leprae. With the purpose of identifying genes of susceptibility, the present study investigated the possible role of HLA-DRB1 and DQA1/DQB1 alleles in susceptibility to leprosy, and whether they account for the heterogeneity in immune responses observed following infection in a Southern Brazilian population. METHODS: One hundred and sixty-nine leprosy patients and 217 healthy controls were analyzed by polymerase chain reaction amplification and reverse hybridization with sequence-specific oligonucleotide probes and sequence-specific primers (One Lambda, CA, USA). RESULTS: There was a positive association of HLA-DRB1*16 (*1601 and *1602) with leprosy per se (7.3% vs. 3.2%, P = 0.01, OR = 2.52, CI = 1.26-5.01), in accord with previous serological studies, which showed DR2 as a marker of leprosy. Although, HLA-DQA1*05 frequency (29.8% vs. 20.9%, P = 0.0424, OR = 1.61, CI = 1.09-2.39) was higher in patients, and HLA-DQA1*02 (3.0% vs. 7.5%, P = 0.0392, OR = 0.39, CI = 0.16 - 0.95) and HLA-DQA1*04 (4.0% vs. 9.1%, P = 0.0314, OR = 0.42, CI = 0.19 - 0.93) frequencies lower, P-values were not significant after the Bonferroni's correction. Furthermore, HLA-DRB1*1601 (9.0% vs. 1.8%; P = 0.0016; OR = 5.81; CI = 2.05-16.46) was associated with susceptibility to borderline leprosy compared to control group, and while HLA-DRB1*08 (11.2% vs. 1.2%; P = 0.0037; OR = 12.00; CI = 1.51 - 95.12) was associated with susceptibility to lepromatous leprosy, when compared to tuberculoid leprosy, DRB1*04 was associated to protection. CONCLUSION: These data confirm the positive association of HLA-DR2 (DRB1*16) with leprosy per se, and the protector effect of DRB1*04 against lepromatous leprosy in Brazilian patients.

Kanazawa N, Mikita N, Li HJ, Nakatani Y, Ozaki M, Kosaka M, et al. Genetic involvement of bacterial sensor molecules in Japanese leprosy. Nihon Hansenbyo Gakkai Zasshi. 2009 Sep; 78(3): 255-61.

Occurrence of new patients of leprosy, caused by Mycobacterium leprae infection, is now almost absent in Japan but is still uncontrolled in developing countries. As one factor affecting the disease development, genetic predisposition of a host has been considered to be associated. Actually, various gene mutations have been reported to be associated at two stages of the disease progression, not only establishment of the disease but also determination of the phenotype, such as lepromatous (L)-type, tuberculoid (T)-type and reversal reaction. On the basis of recent progress of the research on innate immunity, here we analyzed single nucleotide polymorphisms (SNPs) of the genes of major bacterial sensor molecules expressed in antigen-presenting cells, TLR2, DC-SIGN, NOD1 and NOD2, in Japanese leprosy patients. As a result, frequency of polymorphisms in DC-SIGN -336 showed significant difference between the leprosy patients and the healthy controls, reflecting its role in establishment of the disease. Especially, among those with a particular TLR2 -16934 genotype, frequency of the polymorphisms in DC-SIGN -336 showed significant difference between the patients and the controls, suggesting any cooperation of these SNPs

Ribeiro-Guimarães ML, Marengo EB, Tempone AJ, Amaral JJ, Klitzke CF, Silveira EK, et al. Cloning, expression and characterisation of an HtrA-like serine protease produced in vivo by Mycobacterium leprae. Mem Inst Oswaldo Cruz. 2009 Dec; 104(8): 1132-8.

Members of the high temperature requirement A (HtrA) family of chaperone proteases have been shown to play a role in bacterial pathogenesis. In a recent report, we demonstrated that the gene ML0176, which codes for a predicted HtrA-like protease, a gene conserved in other species of mycobacteria, is transcribed by Mycobacterium leprae in human leprosy lesions. In the present study, the recombinant ML0176 protein was produced and its enzymatic properties investigated. M. lepraerecombinant ML0176 was able to hydrolyse a variety of synthetic and natural peptides. Similar to other HtrA proteins, this enzyme displayed maximum proteolytic activity at temperatures above 40 degrees C and was completely inactivated by aprotinin, a protease inhibitor with high selectivity for serine proteases. Finally, analysis of M. leprae ML0176 specificity suggested a broader cleavage preference than that of previously described HtrAs homologues. In summary, we have identified an HtrA-like protease in M. lepraethat may constitute a potential new target for the development of novel prophylactic and/or therapeutic strategies against mycobacterial infections.

Qi W, Käser M, Röltgen K, Yeboah-Manu D, Pluschke G. Genomic diversity and evolution of Mycobacterium ulcerans revealed by next-generation sequencing. PLoS Pathog. 2009 Sep; 5(9): e1000580.

Mycobacterium ulcerans is the causative agent of Buruli ulcer, the third most common mycobacterial disease after tuberculosis and leprosy. It is an emerging infectious disease that afflicts mainly children and youths in West Africa. Little is known about the evolution and transmission mode of M. ulcerans, partially due to the lack of known genetic polymorphisms among isolates, limiting the application of genetic epidemiology. To systematically profile single nucleotide polymorphisms (SNPs), we sequenced the genomes of three M. ulcerans strains using 454 and Solexa technologies. Comparison with the reference genome of the Ghanaian classical lineage isolate Agy99 revealed 26,564 SNPs in a Japanese strain representing the ancestral lineage. Only 173 SNPs were found when comparing Agy99 with two other Ghanaian isolates, which belong to the two other types previously distinguished in Ghana by variable number tandem repeat typing. We further analyzed a collection of Ghanaian strains using the SNPs discovered. With 68 SNP loci, we were able to differentiate 54 strains into 13 distinct SNP haplotypes. The average SNP nucleotide diversity was low (average 0.06-0.09 across 68 SNP loci), and 96% of the SNP locus pairs were in complete linkage disequilibrium. We estimated that the divergence of the M. ulcerans Ghanaian clade from the Japanese strain occurred 394 to 529 thousand years ago. The Ghanaian subtypes diverged about 1000 to 3000 years ago, or even much more recently, because we found evidence that they evolved significantly faster than average. Our results offer significant insight into the evolution of M. ulcerans and provide a comprehensive report on genetic diversity within a highly clonal M. ulcerans population from a Buruli ulcer endemic region, which can facilitate further epidemiological studies of this pathogen through the development of high-resolution tools.

Watson CL, Lockwood DN. Single nucleotide polymorphism analysis of European archaeological M. leprae DNA. PLoS One. 2009 Oct 22; 4(10): e7547.

BACKGROUND: Leprosy was common in Europe eight to twelve centuries ago but molecular confirmation of this has been lacking. We have extracted M. leprae ancient DNA (aDNA) from medieval bones and single nucleotide polymorphism (SNP) typed the DNA, this provides insight into the pattern of leprosy transmission in Europe and may assist in the understanding of M. leprae evolution. METHODS AND FINDINGS: Skeletons have been exhumed from 3 European countries (the United Kingdom, Denmark and Croatia) and are dated around the medieval period (476 to 1350 A.D.). we tested for the presence of 3 previously identified single nucleotide polymorphisms (SNPs) in 10 aDNA extractions. M. leprae aDNA was extracted from 6 of the 10 bone samples. SNP analysis of these 6 extractions were compared to previously analysed European SNP data using the same PCR assays and were found to be the same. Testing for the presence of SNPs in M. leprae DNA extracted from ancient bone samples is a novel approach to analysing European M. leprae DNA and the findings concur with

the previously published data that European M. leprae strains fall in to one group (SNP group 3). CONCLUSIONS: These findings support the suggestion that the M. leprae genome is extremely stable and show that archaeological M. leprae DNA can be analysed to gain detailed information about the genotypic make-up of European leprosy, which may assist in the understanding of leprosy transmission worldwide.

Brochado MJ, Nascimento MM, Louzada Junior P, Figueiredo JF, Roselino AM. [Val247Leu polymorphism of beta2 glycoprotein 1 gene may justify the genesis of anti beta2GP1 antibodies and antiphospholipid syndrome in multibacillary leprosy]. An Bras Dermatol. 2009 Aug; 84(4): 355-9.

BACKGROUND - Multibacillary (MB) leprosy may be manifested with antiphospholipid antibodies (aPL), among which anti-beta2GP1 (beta2-glycoprotein 1). High titers of aPL are associated with APS (Antiphospholipid Syndrome), characterized by thrombosis. The mutation Val247Leu in the domain V of beta2GP1 exposes hidden epitopes with consequent development of anti-beta2GP1 antibodies. OBJECTIVE: To evaluate the Val247Leu polymorphism of beta2GP1 gene and its correlation with anti-beta2GP1 antibodies in leprosy patients. METHODS: The Val247Leu polymorphism was performed by PCR-RFLP and anti-beta2GP1 antibodies were measured by ELISA. RESULTS: The genotypic Val/Val was more prevalent in the leprosy group, compared to controls. Regarding the 7 MB patients with APS, four presented heterozygosis and three, Val/Val homozygosis. Although higher titrations of anti-beta2GP1 IgM antibodies were seen in MB leprosy group with Val/Leu and Val/Val genotypes, there was no statistical difference when compared to Leu/Leu genotype. CONCLUSION: The prevalence of Val/Val homozygosis in leprosy group can partially justify the presence of anti-beta2GP1 IgM antibodies in MB leprosy. The description of heterozygosis and Val/Val homozygosis in 7 patients with MB leprosy and thrombosis corroborates the implication of anomalous phenotype expression of beta2GP1 and development of anti-beta2GP1 antibodies, with consequent thrombosis and APS.

Sakamuri RM, Harrison J, Gelber R, Saunderson P, Brennan PJ, Balagon M, et al. A continuation: study and characterisation of Mycobacterium leprae short tandem repeat genotypes and transmission of leprosy in Cebu, Philippines. Lepr Rev. 2009 Sep; 80(3): 272-9.

OBJECTIVE: To study the stability and allelic diversity of tandem repeat loci in M. leprae in leprosy patients of Cebu, Philippines, and the suitability of multilocus variable number of tandem repeat (VNTR) analysis (MLVA) typing for detecting transmission. METHODS: Seventy newly diagnosed leprosy patients consulting at the Leonard Wood Memorial, Cebu Skin Clinic Total DNA was extracted from slit skin smear (SSS) scrapings of each patient and used for amplification of 13 M. leprae VNTR loci by single locus or multiplex PCR. Number of repeats for each VNTR locus was obtained by DNA sequencing or fragment length analysis methods. Medical, social and geographic details were included in the molecular epidemiology database. RESULTS AND CONCLUSIONS: Multiplex PCR (MP) and fragment length analysis (FLA) methods were found to be more efficient and accurate compared to single short tandem repeat (STR) amplification and DNA sequencing. Intra-patient MLVA patterns from four different samples were conserved in the minisatellites, while differences in one or more of the polymorphic and stutter prone microsatellites was observed, in four of five patients. The 13 loci could differentiate M. leprae strains in Cebu, however, MLVA patterns were stable enough during incubation and transmission between individuals within multi-case families. Thus M. leprae MLVA has potential for strain typing and transmission studies in Cebu.

Cardona-Castro N, Beltrán-Alzate JC, Romero-Montoya IM, Meléndez E, Torres F, Sakamuri RM, et al. Identification and comparison of Mycobacterium leprae genotypes in two geographical regions of Colombia. Lepr Rev. 2009 Sep; 80(3): 316-21.

OBJECTIVE: To evaluate and establish genomic strain typing markers suitable for the identification of transmission patterns of leprosy in different regions of Colombia. DESIGN: Patients from Agua de Dios, Barranquilla and

Cartagena cities and neighbouring towns were enrolled during 2006-2007. Slit skin smears or biopsies were obtained from newly detected untreated patients, and those undergoing multidrug therapy. DNA was extracted from the clinical samples and tested using 15 different short tandem repeat and three SNP polymorphic markers. RESULTS AND CONCLUSION: Differences or similarities between strain types from the northeast (n = 20) and central regions of Colombia (n = 18) were noted. The alleles at two loci, 27-5 and 12-5 were different in the M. leprae in the two regions. The other microsatellite loci may be useful for further intra-population differentiation. There was strong association of 27-5 and 12-5 alleles with the SNP types. The 4-5 combination of alleles was associated with SNP type 3, while the 5-4 combination was mostly associated with SNP type 1, 2 or 4. The SNP type 4 m. leprae isolates were seen in patients in the northeast, but not in the central part.

Xing Y, Liu J, Sakamuri RM, Wang Z, Wen Y, Vissa V, et al. VNTR typing studies of Mycobacterium leprae in China: assessment of methods and stability of markers during treatment. Lepr Rev. 2009 Sep; 80(3): 261-71.

OBJECTIVE: To evaluate the reliability and feasibility of two methods of multilocus variable number of tandem repeat analysis (MLVA) for strain typing of M. leprae, and to study whether short tandem repeat loci are stable and suitable for epidemiological study of leprosy. METHODS: Total DNA was extracted from skin biopsies of 20 new multibacillary (MB) patients from China diagnosed in 2006. To determine the copy numbers of short tandem repeats (STRs) for 13 loci, we amplified each locus individually by PCR, followed by sequence analysis of the amplicons. Separately, the same loci, plus four others were amplified by Multiplex PCRs (MP) using fluorescent primers and the copy number was identified by fragment length analysis (MP-FLA). MLVA was also performed at different times during treatment for a subset of the patients. RESULTS AND CONCLUSIONS: Genetic variability of M. leprae in China can be assessed in microsatellite loci. (GTA)9 and (TTC)21 loci are hypervariable, with array sizes of 25 repeat units or more. The expansion of the (GTA)9 locus is a characteristic of some M. leprae isolates in China. A high level of allele concordance was observed between PCR-sequencing and MP-FLA methods. However, MP-FLA method was cost-effective, rapid, high throughput and suitable for strain typing. Five of the 20 isolates of M. leprae were from patients residing in the same township in Qiubei County, Yunnan, and matched closely by MLVA. Three of these patients are family contacts of previously diagnosed patients, with intra-familial strain types being similar, suggesting infections from common sources and transmission chain(s). The VNTR patterns were highly similar in biopsy and slit skin smears (SSS) before treatment, and in the SSS collected at various time points during treatment. Taken together, VNTR strain typing is a useful tool for study of short range transmission in leprosy.

Matsuoka M, Gonzalez AV, Estrada I, Carreño-Martinez C, Fafutis-Morris M. Various genotypes of Mycobacterium leprae from Mexico reveal distinct geographic distribution. Lepr Rev. 2009 Sep; 80(3): 322-6.

OBJECTIVE: To classify Mycobacterium leprae isolates from multiple areas in Mexico based on variable number of tandem repeats of 6 base within the rpoT gene and three single nucleotide polymorphism (SNP), and to analyse their geographic distribution in the context of the origin of leprosy in Mexico. RESULTS: Analysis for rpoT genotyping of 64 samples collected in the west and southwestern areas revealed that 46 isolates were of the 4 copy type and 18 isolates were of the 3 copy type. All samples from the eastern coastal area (n = 24) and from the Yucatan peninsula (n = 12) were of the 3 copy type. Six isolates from the west and southwestern area were SNP-type 1, 13 isolates were SNP-type 2 and 45 isolates were SNP-type 3. Nineteen of 24 isolates from the eastern coastal area were SNP-type 3 and one was SNP-type 4. Seven isolates from the Yucatan peninsula were SNP-type 3 and one was SNP-type 4. CONCLUSION: The difference of the proportion of each genotype between the western areas and the eastern areas indicated the expansion of leprosy through different paths in Mexico.

Fontes AN, Sakamuri RM, Baptista IM, Ura S, Moraes MO, Martínez AN, et al. Genetic diversity of mycobacterium leprae isolates from Brazilian leprosy patients. Lepr Rev. 2009 Sep; 80(3): 302-15.

INTRODUCTION: Leprosy is a chronic disease caused by infection with Mycobacterium leprae, an obligate intracellular parasite. A problem in studying the transmission of leprosy is the small amount of variation in bacterial genomic DNA. The discovery of variable number of tandem repeats (VNTRs) allowed the detection of strain variation in areas with a high prevalence of leprosy. Four genotypes of M. leprae based on three single-nucleotide polymorphism (SNPs) were also discovered to be useful for analysis of the global spread of leprosy. METHODS: In this present study, we examined the allelic diversity of M. leprae at 16 select VNTR and three SNP loci using 89 clinical isolates obtained from patients mainly from the neighbouring states of São Paulo and Rio de Janeiro Brazil. RESULTS AND CONCLUSION: By use of a PCR-RFLP-based procedure that allows the recognition of SNP types 3 and 4 without the need for the more expensive DNA sequencing steps, characterisation of the main M. leprae genotypes was easy. When applied on the study population, it was found that the SNP type 3 is most frequent in these two states of Brazil, and that VNTRs provided further discrimination of the isolates. Two Short Tandem Repeats (STRs) were monomorphic, with the remaining 14 STRs represented by two to 18 alleles. Epidemiological associations with township or state were not evident in this random collection and require further investigations. In phylogenetic trees, branches formed by all 16 STRs clearly separated SNP type 3 organisms from the other types while the allelic patterns of two minisatellite loci 27-5 and 12-5 were highly correlated with SNP type 3. This strain typing study provide the basis for comparison of M. leprae strain types within Brazil and with those from other countries, and informed selection of genomic markers and methods for future studies.

Shinde V, Newton H, Sakamuri RM, Reddy V, Jain S, Joseph A, et al. VNTR typing of Mycobacterium leprae in South Indian leprosy patients. Lepr Rev. 2009 Sep; 80(3): 290-301.

OBJECTIVES: To study the suitability, stability and diversity of short tandem repeat (STR) genomic markers to elicit strain variation in the Mycobacterium leprae isolates within leprosy patients from Andhra Pradesh and Tamil Nadu states in South India. MATERIALS AND METHODS: Slit skin smear (SSS) samples were collected from lesions and various body sites of newly diagnosed leprosy patients. The SSSs from each patient were pooled, except in the case of five patients. Total DNA was extracted from SSS samples. M. leprae STRs were amplified from the DNA either by multiplex PCR (MP) or single PCR methods. The number of repeats for each STR locus (the STR allele) was obtained either by fragment length analysis (FLA) or by DNA sequencing of the PCR amplicons. RESULTS AND CONCLUSION: Multiplex PCR minimised the use of DNA and reagents, and together with FLA, was time and cost effective for STR strain typing. After examination of the isolates of South Indian origin at 13 STR loci, it was determined that the alleles for (AC)8b, (GGT)5, 6-3a (rpoT), 21-3, 27-5, and 23-3 were conserved in two study populations. In a family from Andhra Pradesh, the M. leprae STR patterns in two patients were identical in 16 of 18 loci which indicate a common source of infection. Fourteen of 15 STR loci showed no intra-patient variation in the five patients tested in Tamil Nadu. Altogether, these studies indicate the suitability of STR strain typing for assessing short-range transmission chains.

Gillis T, Vissa V, Matsuoka M, Young S, Richardus JH, Truman R, et al. Ideal Consortium Partners. Characterisation of short tandem repeats for genotyping Mycobacterium leprae. Lepr Rev. 2009 Sep; 80(3): 250-60.

OBJECTIVE: Establish a typing system for Mycobacterium leprae based on polymorphic DNA structures known as short tandem repeats (STR). DESIGN: Assess 16 polymorphic STR for sensitivity, specificity and reproducibility in standard assays using reference strains of M. leprae. RESULTS: Primers for 16 STR loci were selected based on

PCR product size and for their ability to sequence each STR locus from both directions. All primer pairs produced a visible PCR amplicon of appropriate size from PCR reactions containing 10 M. leprae cells. DNA sequences for each STR locus, except (AT) 15, was correctly identified as M. leprae-specific in replicate samples containing 1000 M. leprae using either the forward or reverse PCR primers. Twelve of 13 M. leprae STR loci were stable during passage in heavily infected armadillo tissues over a 5 year and 7 month infection cycle. CONCLUSIONS: Certain M. leprae STR provide suitable targets for strain typing with the potential for grouping M. leprae with shared genotypes that may prove useful for establishing linkages between leprosy cases within geographical regions.

Zhang F, Liu H, Chen S, Wang C, Zhu C, Zhang L, et al. Evidence for an association of HLA-DRB1*15 and DRB1*09 with leprosy and the impact of DRB1*09 on disease onset in a Chinese Han population. BMC Med Genet. 2009 Dec 11;10: 133.

Human leukocyte antigens (HLAs) have been proposed to modulate the immune response to Mycobacterium leprae. The association of HLA-DRB1 with leprosy has been reported in several populations, but not in a Chinese population. METHODS: The polymerase chain reaction-sequence-specific oligonucleotide probe with Luminex100 (PCR-SSOP-Luminex) method was used to genotype HLA-DRB1 alleles in 305 leprosy patients and 527 healthy control individuals. RESULTS: The HLA-DRB1*15 allele was significantly more prevalent among leprosy patients than healthy controls, whereas the frequency of the HLA-DRB1*09 allele was lower among leprosy patients, especially those with early-onset disease. CONCLUSION: HLA-DRB1 alleles are associated with leprosy susceptibility in a Chinese population. The HLA-DRB1*09 allele was found to be protective exclusively in a subset of early-onset leprosy patients.

Sharma R, Lavania M, Chauhan DS, Katoch K, Katoch VM. Potential of a metabolic gene (accA3) of M. leprae as a marker for leprosy reactions. Indian J Lepr. 2009 Jul-Sep; 81(3): 141-8.

Understanding the mechanism(s) of reactions in leprosy remains a challenging task for both clinicians and basic scientists. While there is some understanding of host processes associated with different type of lepra reactions, there is very little information about bacterial factors triggering these inflammatory processes. This study is continuation of our earlier research programme on leprosy genomics in which significant transcription of 11 genes was observed during active disease and these included accA3 gene. In present study, we have investigated the potential of this gene or its gene product as molecular and or immunological marker for studying the reactions. Using quantitative Real-Time RT-PCR significant higher expression (mean log2 ratio=3.39) of accA3 was observed in specimens from leprosy reaction cases compared with cases without reactions. in silico homology model of this protein was analyzed for hydrophilic and B-cell epitope regions. Peptides with maximum antigenecity were selected, cloned, expressed and used to study sero-reactivity across the disease spectrum by indirect ELISA. While sero-reactivity was observed in leprosy cases the antibody levels did not vary significantly between the patient/s of same clinical type with and without reaction thereby indicating the limitation of this approach for this purpose. Measurement of transcription of this gene has, thus, potential as a molecular marker for monitoring the reactions.

Lavania M, Lal R, Joseph G, Darlong J, Abraham S, Nanda NK, Jadhav RS. Genotypic analysis of Mycobacterium leprae strains from different regions of India on the basis of rpoT. Indian J Lepr. 2009 Jul-Sep; 81(3): 119-24.

Mycobacterium leprae strains from Indian leprosy patients were analyzed using the six base tandem repeat, GACATC, in rpoT gene as genetic marker. DNA was extracted from slit-skin smears and nasal swabs of new untreated as well as treated leprosy patients living in dif-

ferent regions of India. PCR amplification of rpoT gene and sequencing of amplicons showed the presence of two genotype of M. leprae in this study, 73.4% having three copies (ancient Indian type) and 26.6% contain 4 copies (considered to be Japanese and Korean). These genotypes along with other short tandem repeats may help in studying the historical spread of disease and the strains of M. leprae disseminated by various human races that migrated to India from other places of Asia and European countries during our history

HANSENÍASE EXPERIMENTAL

Gelber R, Andries K, Paredes RM, Andaya CE, Burgos J. The diarylquinoline R207910 is bactericidal against Mycobacterium leprae in mice at low dose and administered intermittently. Antimicrob Agents Chemother. 2009 Sep; 53(9): 3989-91.

The diarylquinoline R207910 is profoundly bactericidal in a murine model of tuberculosis. Previously, R207910 was also found to be bactericidal for Mycobacterium leprae-infected mice during lag phase. Herein we evaluate the bactericidal efficacy of R207910 (1 to 120 mg/kg of body weight) when administered five times weekly, once weekly, and once monthly during logarithmic multiplication of M. leprae organisms. All treatments were found to be bactericidal, suggesting that both low and intermittent dosing with R207910 holds promise for leprosy patients.

Cardona-Castro N, Beltrán JC, Ortiz-Bernal A, Vissa V. Detection of Mycobacterium leprae DNA in nine-banded armadillos (Dasypus novemcinctus) from the Andean region of Colombia. Lepr Rev. 2009 Dec; 80(4): 424-31.

OBJECTIVE: To use DNA detection methodologies to test for M. leprae in nine-banded armadillos inhabiting forested regions located around the cities and towns where leprosy patients have been identified. DESIGN: Ear lobe biopsies of 22 nine-banded armadillos were studied during a 2 year period. The biopsies were processed for DNA extraction and amplification by nested polymerase chain reaction (N-PCR) of a fragment of the high copy DNA locus of M. leprae known as R-LEP. RESULTS: Nine of the 22 (40.9%) armadillos evaluated showed positive signals for M. leprae. Sequencing confirmed that PCR products were identical to the corresponding region of M. leprae DNA. CONCLUSIONS: In Colombia, South America, the consumption of and contact with the nine-banded armadillo (Dasypus novemcinctus) are common, ignoring the fact that this animal can host and be a possible zoonotic reservoir of Mycobacterium leprae, the causal agent of leprosy. This is the first study demonstrating that M. leprae is present in nine-banded armadillos in a region of Colombia using specific DNA detection. The possibility of leprosy transmission due to contact and consumption of armadillo meat or use of blood for therapeutic purposes should be further investigated.

HISTÓRIA

Hirai Y. Kensuke Mitsuda and his memory of the "Kaishun Byoshitsu" days: why did he not clearly state the time of its foundation? Nippon Ishigaku Zasshi. 2009 Dec; 55(4): 445-61.

The author, in a previous paper, has argued that there is no hard evidence to show that the foundation of the "Kaishun Byoshitsu" in the Tokyo City Yoikuin (poorhouse) was in 1899. In developing the conclusion, this article, first, estimates the correct time of the founding the facility and, second, analyzes the reasons for confusing the verbal evidence of Kensuke Mitsuda that led to the prevalence of the incorrect story. As to the former, it is an undoubted fact that the founding year was 1901 or 1902, as the author has checked the career of Koto Ishiwata, a nurse who exclusively served the Kaishun Byoshitsu, and the documents which shows a historical change in layout and floor space of its rooms. As for the latter, by reviewing "the medical staff" system of the yoikuin (poorhouse), the author shows the background of Mitsuda's unfortunate days when he served there. The author finally suggests that Mitsuda's inferiority feelings about his misfortune might have caused his disordered testimonies, in other words, "an artificial memory".

IMUNOLOGIA

Bochud PY, Sinsimer D, Aderem A, Siddiqui MR, Saunderson P, Britton S, et al. Polymorphisms in Toll-like receptor 4 (TLR4) are associated with protection against leprosy. Eur J Clin Microbiol Infect Dis. 2009 Sep;28(9):1055-65. Epub 2009 May 9.

Accumulating evidence suggests that polymorphisms in Toll-like receptors (TLRs) influence the pathogenesis of mycobacterial infections, including leprosy, a disease whose manifestations depend on host immune responses. Polymorphisms in TLR2 are associated with an increased risk of reversal reaction, but not susceptibility to leprosy itself. We examined whether polymorphisms in TLR4 are associated with susceptibility to leprosy in a cohort of 441 Ethiopian leprosy patients and 197 healthy controls. We found that two single nucleotide polymorphisms (SNPs) in TLR4 (896G>A [D299G] and 1196C>T [T399I]) were associated with a protective effect against the disease. The 896GG, GA and AA genotypes were found in 91.7, 7.8 and 0.5% of leprosy cases versus 79.9, 19.1 and 1.0% of controls, respectively (odds ratio [OR] = 0.34, 95% confidence interval [CI] 0.20-0.57, P < 0.001, additive model). Similarly, the 1196CC, CT and TT genotypes were found in 98.1, 1.9 and 0% of leprosy cases versus 91.8, 7.7 and 0.5% of controls, respectively (OR = 0.16, 95% CI 0.06--.40, P < 0.001, dominant model). We found that Mycobacterium leprae stimulation of monocytes partially inhibited their subsequent response to lipopolysaccharide (LPS) stimulation. Our data suggest that TLR4 polymorphisms are associated with susceptibility to leprosy and that this effect may be mediated at the cellular level by the modulation of TLR4 signalling by M. leprae.

Bührer-Sékula S, Illarramendi X, Teles RB, Penna ML, Nery JA, Sales AM, et al. The additional benefit of the ML Flow test to classify leprosy patients. Acta Trop. 2009 Aug;111(2): 172-6.

The use of the skin lesion counting classification leads to both under and over diagnosis of leprosy in many instances. Thus, there is a need to complement this classification with another simple and robust test for use in the field. Data of 202 untreated leprosy patients diagnosed at FIOCRUZ, Rio de Janeiro, Brazil, was analyzed. There were 90 patients classified as PB and 112 classified as MB according to the reference standard. The BI was positive in 111 (55%) patients and the ML Flow test in 116 (57.4%) patients. The ML Flow test was positive in 95 (86%) of the patients with a positive BI. The lesion counting classification was confirmed by both BI and ML Flow tests in 65% of the 92 patients with 5 or fewer lesions, and in 76% of the 110 patients with 6 or more lesions. The combination of skin lesion counting and the ML Flow test results yielded a sensitivity of 85% and a specificity of 87% for MB classification, and correctly classified 86% of the patients when compared to the standard reference. A considerable proportion of the patients (43.5%) with discordant test results in relation to standard classification was in reaction. The use of any classification system has limitations, especially those that oversimplify a complex disease such as leprosy. In the absence of an experienced dermatologist and slit skin smear, the ML Flow test could be used to improve treatment decisions in field conditions.

Franceschi DS, Mazini PS, Rudnick CC, Sell AM, Tsuneto LT, Ribas ML, et al. Influence of TNF and IL10 gene polymorphisms in the immunopathogenesis of leprosy in the south of Brazil. Int J Infect Dis. 2009 Jul;13(4): 493-8.

OBJECTIVE: To determine whether cytokine polymorphisms are associated with leprosy and/or their subtypes in a Brazilian population. METHODS: Genotyping using polymerase chain reaction with sequence-specific primers (PCR-SSP) was performed for: TNF(-308/-238), IL2(-330/+166), IL6(-174), IFNG(+874), TGFB1(+869/+915), and IL10(-592/-819/-1082) in 240 healthy controls and 167 patients with leprosy. RESULTS: For TNF(-308), a higher frequency of GG genotype (85.5% vs. 74.1% in healthy controls, p = 0.009), along with a decreased frequency of GA/AA genotypes was observed among leprosy patients as compared to the control group (14.5% vs. 25.9%, p = 0.009). The GG genotype was particularly higher in patients with tuberculoid (TT) and borderline (BB) leprosy (90.5% and 89.8%, respectively). Analysis of

IL10 genotypes revealed a lower frequency of GCC/GCC haplotype in lepromatous leprosy (LL) patients (6.2%) in comparison to controls (15.4%). CONCLUSION: It is suggested that the G-->A substitution at position -308 in the TNF promoter region plays an important role in leprosy patients.

Maeda Y, Tamura T, Matsuoka M, Makino M. Inhibition of the multiplication of Mycobacterium leprae by vaccination with a recombinant M. bovis BCG strain that secretes major membrane protein II in mice. Clin Vaccine Immunol. 2009 Oct; 16(10): 1399-404.

The ability of a recombinant Mycobacterium bovis BCG strain that secretes major membrane protein II (MMP-II) of Mycobacterium leprae (BCG-SM) to confer protection against leprosy was evaluated by use of a mouse footpad model. C57BL/6J mice intradermally inoculated with BCG-SM produced splenic T cells which secreted significant amounts of gamma interferon (IFN-gamma) in response to either the recombinant MMP-II, the M. leprae-derived membrane fraction, or the BCG-derived cytosolic fraction in vitro more efficiently than those from the mice infected with the vector control BCG strain (BCG-pMV, a BCG strain containing pMV-261). A higher percentage of CD8(+) T cells obtained from BCG-SM-inoculated mice than those obtained from BCG-pMV-inoculated mice produced intracellular IFN-gamma on restimulation with the M. leprae antigens. BCG-SM inhibited the multiplication of M. leprae in the footpads of C57BL/6J mice more efficiently than BCG-pMV. These results indicate that a BCG strain that secretes MMP-II could be a better vaccine candidate for leprosy.

Mitra DK, Joshi B, Dinda AK, Rai AK, Girdhar BK, Katoch K, et al. Induction of lepromin reactivity in cured lepromatous leprosy patients: impaired chemokine response dissociates protective immunity from delayed type hypersensitivity. Microbes Infect. 2009 Dec;11(14-15):1122-30.

Delayed Type Hypersensitivity (DTH) and protective immunity are thought to be tightly linked. Remarkable similarity exists between their cellular and immune mechanisms. However, their dissociation is also well known. Here we investigate the immunological mechanisms relevant for their dissociation in a group of non-relapsing cured lepromatous leprosy (CLL) patients. In these patients, using lepromin reaction as a model system of DTH we report critical role of tissue chemokine response in synchronous manifestation of these linked phenomena. Results indicate elevation of the threshold of tissue chemokine induction thus dissociating DTH from protective immunity in lepromin -ive CLL patients. We also show that the DTH anergy in these subjects is not an absolute one but depends on the strength of the stimulus. Our data provide insights into the intricate relationship between DTH and immunity and highlight the persistent presence of effector immune mechanisms involving these two pathways in apparently unresponsive lepromatous leprosy patients.

Parkash O, Singh BP, Pai M. Regions of differences encoded antigens as targets for immunodiagnosis of tuberculosis in humans. Scand J Immunol. 2009 Oct; 70(4): 345-57.

Tuberculosis is one of the major global health problems causing nearly 2 million deaths every year. It continues to be a leading cause of morbidity and mortality in developing countries. Accurate early diagnosis and proper treatment can control the spread of tuberculosis in the community. Currently used diagnostic tests have certain limitations such as low sensitivity and suboptimal turnaround times. Hence, introduction of diagnostic methods that are comparatively more sensitive and specific can increase the efficiency of strategies to control tuberculosis. In recent years, there has been a remarkable progress in identifying new and potentially useful antigens for diagnosis of both latent and active tuberculosis. Regions of differences (RD) encoded proteins are among such promising candidate antigens (RD antigens). Some of these antigens are encoded by regions of differences located in the genome of Mycobacterium tuberculosis, M. africanum, M. bovis but are absent in all the Bacillus Calmette Guerin substrains and many of the environmental mycobacteria. Over the past few years, RD antigens,

particularly RD-based diagnostic methods such as improved tuberculin skin testing, interferon-gamma release assays, and RD1-based serological assays are being tested and have shown promising results. This article provides an overview of the use of RD antigens in the immunodiagnosis of tuberculosis infection and disease.

Zenha EM, Ferreira MA, Foss NT. Use of anti-PGL-1 antibodies to monitor therapy regimes in leprosy patients. Braz J Med Biol Res. 2009 Oct; 42(10): 968-72.

The suitability of IgM antibodies to PGL-1 for monitoring the response to multidrug therapy (MDT) was sequentially tested by ELISA in 105 leprosy patients, and bacterial indexes (BI) were also determined. Patients were divided into 3 groups: group 1, 34 multibacillary (MB) patients treated for 12 months with MDT-MB; group 2, 33 MB patients treated for 24 months with MDT-MB, and group 3, 38 paucibacillary (PB) patients treated for 6 months with MDT-PB. Untreated MB patients exhibited higher antibody levels (mean +/- SEM): group 1 (6.95 +/- 1.35) and group 2 (12.53 +/- 2.02) than untreated PB patients (1.28 +/- 0.35). There was a significant difference ($P < 0.01$) in anti-PGL-1 levels in group 1 patients: untreated (6.95 +/- 1.35) and treated for 12 months (2.78 +/- 0.69) and in group 2 patients: untreated (12.53 +/- 2.02) and treated for 24 months (2.62 +/- 0.79). There was no significant difference between untreated (1.28 +/- 0.35) and treated (0.62 +/- 0.12) PB patients. Antibody levels correlated with BI. The correlation coefficient (Pearson's r) was 0.72 before and 0.23 ($P < 0.05$) after treatment in group 1 and 0.67 before and 0.96 ($P < 0.05$) after treatment in group 2. BI was significantly reduced ($P < 0.01$) after 12 and 24 months on MDT (group 1: 1.26-0.26; group 2: 1.66-0.36). Our data indicate that monitoring anti-PGL-1 levels during MDT may be a sensitive tool for evaluating treatment efficacy. These data also indicate that the control of leprosy infection can be obtained with 12 months of MDT in MB patients.

Raman VS, O'Donnell J, Bailor HR, Goto W, Lahiri R, Gillis TP,et al. Vaccination with the ML0276 antigen reduces local inflammation but not bacterial burden during experimental Mycobacterium leprae infection. Infect Immun. 2009 Dec; 77(12): 5623-30.

Leprosy elimination has been a goal of the WHO for the past 15 years. Widespread BCG vaccination and multidrug therapy have dramatically reduced worldwide leprosy prevalence, but new case detection rates have remained relatively constant. These data suggest that additional control strategies, such as a subunit vaccine, are required to block transmission and to improve leprosy control. We recently identified several Mycobacterium leprae antigens that stimulate gamma interferon (IFN-gamma) secretion upon incubation with blood from paucibacillary leprosy patients, a group who limit M. leprae growth and dissemination. In this study, we demonstrate that M. leprae-specific mouse T-cell lines recognize several of these antigens, with the ML0276 protein stimulating the most IFN-gamma secretion. We then examined if the ML0276 protein could be used in a subunit vaccine to provide protection against experimental M. leprae infection. Our data demonstrate that combining ML0276 with either a Toll-like receptor 4 (TLR4) (EM005), TLR7 (imiquimod), or TLR9 (CpG DNA) agonist during immunization induces Th1 responses that limit local inflammation upon experimental M. leprae infection. Our data indicate that only the ML0276/EM005 regimen is able to elicit a response that is transferable to recipient mice. Despite the potent Th1 response induced by this regimen, it could not provide protection in terms of limiting bacterial growth. We conclude that EM005 is the most potent adjuvant for stimulating a Th1 response and indicate that while a subunit vaccine containing the ML0276 protein may be useful for the prevention of immune pathology during leprosy, it will not control bacterial burden and is therefore unlikely to interrupt disease transmission.

Tamura T, Fukutomi Y, Makino M. Forefront of vaccine development: tuberculosis and leprosy. Nihon Hansenbyo Gakkai Zasshi. 2009 Sep; 78(3): 271-6.

The role of vaccines to tuberculosis and leprosy is to induce a cellular immunity, and as a result to induce the

differentiation of memory CD8+ cytotoxic T cells. 'Help' from CD4+ T cells is important for the differentiation of naive CD8+ T cells to effector and memory CD8+ cytotoxic T cells. However, how CD4+ T cell 'help' is involved in the steps instructing T helper (Th) polarization is not yet clear. Peptide-25, a major Th epitope of Ag85B from Mycobacterium tuberculosis, preferentially induced development of Th1 cells. In contrast, altered peptide ligands (APL) that have a substitution of glycine for alanine at position 248 of Peptide-25 induced solely Th2 development. To elucidate the role of Th polarization on the 'Help' function of CD4+ T cells, we established an in vitro culture system using OVA specific CD8+ T cells, Peptide-25 specific CD4+ T cells and splenic dendritic cells (DCs). The DCs that were pre-cultured with Peptide-25 specific CD4+ T cells together with OVA and Peptide-25 induced the proliferation and granzyme B production of OVA specific CD8+ T cells. On the other hand, the DCs that were pre-cultured with Peptide-25 specific CD4+ T cells together with OVA and APL induced only proliferation of OVA specific CD8+ T cells. These results suggest that Th1 immune response induced by Peptide-25 plays an important role in the induction of functional activation of CD8+ cytotoxic T cells

Montoya D, Cruz D, Teles RM, Lee DJ, Ochoa MT, Krutzik SR, et al. Divergence of macrophage phagocytic and antimicrobial programs in leprosy. Cell Host Microbe. 2009 Oct 22; 6(4): 343-53.

Effective innate immunity against many microbial pathogens requires macrophage programs that upregulate phagocytosis and direct antimicrobial pathways, two functions generally assumed to be coordinately regulated. We investigated the regulation of these key functions in human blood-derived macrophages. Interleukin-10 (IL-10) induced the phagocytic pathway, including the C-type lectin CD209 and scavenger receptors, resulting in phagocytosis of mycobacteria and oxidized low-density lipoprotein. IL-15 induced the vitamin D-dependent antimicrobial pathway and CD209, yet the cells were less phagocytic. The differential regulation of macrophage functional programs was confirmed by analysis of leprosy lesions: the macrophage phagocytosis pathway was prominent in the clinically progressive, multibacillary form of the disease, whereas the vitamin D-dependent antimicrobial pathway predominated in the self-limited form and in patients undergoing reversal reactions from the multibacillary to the self-limited form. These data indicate that macrophage programs for phagocytosis and antimicrobial responses are distinct and differentially regulated in innate immunity to bacterial infections.

Mukai T, Maeda Y, Tamura T, Matsuoka M, Tsukamoto Y, Makino M. Induction of cross-priming of naive CD8+ T lymphocytes by recombinant bacillus Calmette-Guerin that secretes heat shock protein 70-major membrane protein-II fusion protein. J Immunol. 2009 Nov 15; 183(10): 6561-8.

Because Mycobacterium bovis bacillus Calmette-Guérin (BCG) unconvincingly activates human naive CD8(+) T cells, a rBCG (BCG-70M) that secretes a fusion protein comprising BCG-derived heat shock protein (HSP)70 and Mycobacterium leprae-derived major membrane protein (MMP)-II, one of the immunodominant Ags of M. leprae, was newly constructed to potentiate the ability of activating naive CD8(+) T cells through dendritic cells (DC). BCG-70M secreted HSP70-MMP-II fusion protein in vitro, which stimulated DC to produce IL-12p70 through TLR2. BCG-70M-infected DC activated not only memory and naive CD8(+) T cells, but also CD4(+) T cells of both types to produce IFN-gamma. The activation of these naive T cells by BCG-70M was dependent on the MHC and CD86 molecules on BCG-70M-infected DC, and was significantly inhibited by pretreatment of DC with chloroquine. Both brefeldin A and lactacystin significantly inhibited the activation of naive CD8(+) T cells by BCG-70M through DC. Thus, the CD8(+) T cell activation may be induced by cross-presentation of Ags through a TAP- and proteosome-dependent cytosolic pathway. When naive CD8(+) T cells were stimulated by BCG-70-M-infected DC in the presence of naive CD4(+) T cells, CD62L(low)CD8(+) T cells and perforin-producing CD8(+) T cells were efficiently produced. MMP-II-reactive CD4(+) and CD8(+) memory T cells were efficiently produced in C57BL/6 mice by infection with BCG-70M. These results indicate that BCG-70M activated DC, CD4(+) T cells, and

CD8(+) T cells, and the combination of HSP70 and MMP-II may be useful for inducing better T cell activation.

Mattos KA, D'Avila H, Rodrigues LS, Oliveira VG, Sarno EN, Atella GC, et al. Lipid droplet formation in leprosy: Toll-like receptor-regulated organelles involved in eicosanoid formation and Mycobacterium leprae pathogenesis. J Leukoc Biol. 2010 Mar; 87(3): 371-84.

A hallmark of LL is the accumulation of Virchow's foamy macrophages. However, the origin and nature of these lipids, as well as their function and contribution to leprosy disease, remain unclear. We herein show that macrophages present in LL dermal lesions are highly positive for ADRP, suggesting that their foamy aspect is at least in part derived from LD (also known as lipid bodies) accumulation induced during ML infection. Indeed, the capacity of ML to induce LD formation was confirmed in vivo via an experimental model of mouse pleurisy and in in vitro studies with human peripheral monocytes and murine peritoneal macrophages. Furthermore, infected cells were shown to propagate LD induction to uninfected, neighboring cells by generating a paracrine signal, for which TLR2 and TLR6 were demonstrated to be essential. However, TLR2 and TLR6 deletions affected LD formation in bacterium-bearing cells only partially, suggesting the involvement of alternative receptors of the innate immune response besides TLR2/6 for ML recognition by macrophages. Finally, a direct correlation between LD formation and PGE(2) production was observed, indicating that ML-induced LDs constitute intracellular sites for eicosanoid synthesis and that foamy cells may be critical regulators in subverting the immune response in leprosy.

Teles RM, Teles RB, Amadeu TP, Moura DF, Mendonça-Lima L, Ferreira H, et al. High matrix metalloproteinase production correlates with immune activation and leukocyte migration in leprosy reactional lesions. Infect Immun. 2010 Mar; 78(3):1012-21.

Gelatinases A and B (matrix metalloproteinase 2 [MMP-2] and MMP-9, respectively) can induce basal membrane breakdown and leukocyte migration, but their role in leprosy skin inflammation remains unclear. In this study, we analyzed clinical specimens from leprosy patients taken from stable, untreated skin lesions and during reactional episodes (reversal reaction [RR] and erythema nodosum leprosum [ENL]). The participation of MMPs in disease was suggested by (i) increased MMP mRNA expression levels in skin biopsy specimens correlating with the expression of gamma interferon (IFN-gamma) and tumor necrosis factor alpha (TNF-alpha), (ii) the detection of the MMP protein and enzymatic activity within the inflammatory infiltrate, (iii) increased MMP levels in patient sera, and (iv) the in vitro induction of MMP-9 by Mycobacterium leprae and/or TNF-alpha. It was observed that IFN-gamma, TNF-alpha, MMP-2, and MMP-9 mRNA levels were higher in tuberculoid than lepromatous lesions. In contrast, interleukin-10 and tissue inhibitor of MMP (TIMP-1) message were not differentially modulated. These data correlated with the detection of the MMP protein evidenced by immunohistochemistry and confocal microscopy. When RR and ENL lesions were analyzed, an increase in TNF-alpha, MMP-2, and MMP-9, but not TIMP-1, mRNA levels was observed together with stronger MMP activity (zymography/in situ zymography). Moreover, following in vitro stimulation of peripheral blood cells, M. leprae induced the expression of MMP-9 (mRNA and protein) in cultured cells. Overall, the present data demonstrate an enhanced MMP/TIMP-1 ratio in the inflammatory states of leprosy and point to potential mechanisms for tissue damage. These results pave the way toward the application of new therapeutic interventions for leprosy reactions.

Duthie MS, Hay MN, Morales CZ, Carter L, Mohamath R, Ito L, et al. Rational design and evaluation of a multiepitope chimeric fusion protein with the potential for leprosy diagnosis. Clin Vaccine Immunol. 2010 Feb; 17(2): 298-303.

Despite the reduction in the number of leprosy cases registered worldwide as a result of the widespread use of multidrug therapy, the number of new cases detected each year remains stable in many countries. This indicates that Mycobacterium leprae, the causative agent

of leprosy, is still being transmitted and that, without an earlier diagnosis, transmission will continue and infection will remain a health problem. The current means of diagnosis of leprosy is based on the appearance of clinical symptoms, which in many cases occur after significant and irreversible nerve damage has occurred. Our recent work identified several recombinant antigens that are specifically recognized by leprosy patients. The goal of the present study was to produce and validate the reactivity of a chimeric fusion protein that possesses the antibody binding properties of several of these proteins. The availability of such a chimeric fusion protein will simplify future test development and reduce production costs. We first identified the antibody binding regions within our top five antigen candidates by performing enzyme-linked immunosorbent assays with overlapping peptides representing the amino acid sequences of each protein. Having identified these regions, we generated a fusion construct of these components (protein advances diagnostic of leprosy [PADL]) and demonstrated that the PADL protein retains the antibody reactivity of the component antigens. PADL was able to complement a protein that we previously produced (the leprosy IDRI [Infectious Disease Research Institute] diagnostic 1 [LID-1] protein) to permit the improved diagnosis of multibacillary leprosy and that had a good ability to discriminate patients with multibacillary leprosy from control individuals. A serological diagnostic test consisting of these antigens could be applied within leprosy control programs to reduce transmission and to limit the appearance of leprosy-associated disabilities and stigmatizing deformities by directing treatment.

Sharma A, Gupta R, Khaira A, Gupta A, Tiwari SC, Dinda AK. Renal involvement in leprosy: report of progression from diffuse proliferative to crescentic glomerulonephritis. Clin Exp Nephrol. 2010 Jun;14(3): 268-71.

Renal involvement in leprosy has been reported rarely in the literature. Acute kidney injury in patients with leprosy is uncommon and may occur due to acute tubular necrosis, drug-induced interstitial nephritis and rarely crescentic glomerulonephritis. The latter with histologic confirmation of the diagnosis has been reported in very few cases of leprosy. A 25-year-old male, on therapy for multibacillary leprosy, was found to have deranged renal functions on evaluation for a history of nausea, vomiting, swelling and episode of haematuria. Kidney biopsy was performed twice over a period of 2 weeks, showing progression from diffuse proliferative glomerulonephritis to crescentic glomerulonephritis, pauci-immune in nature. The patient was treated aggressively with intravenous steroids, following which his renal functions stabilized. Crescentic glomerulonephritis, an extremely rare phenomenon in leprosy, should be considered in these patients presenting with features of acute kidney injury. Timely performed renal biopsy assists in accurate diagnosis and appropriate management of the patient, hence preserving renal parenchyma. Rapid progression from diffuse proliferative glomerulonephritis to crescentic glomerulonephritis in a patient with leprosy is described herein for the first time in the literature.

Dagur PK, Sharma B, Kumar G, Khan NA, Katoch VM, Sengupta U, Joshi B. Mycobacterial antigen(s) induce anergy by altering TCR- and TCR/CD28-induced signalling events: insights into T-cell unresponsiveness in leprosy. Mol Immunol. 2010 Feb; 47(5): 943-52

Present study investigates the role of Mycobacterium leprae (M. leprae) antigens on TCR- and TCR/CD28-induced signalling leading to T-cell activation and further correlates these early biochemical events with T-cell anergy, as prevailed in advanced stages of leprosy. We observed that both whole cell lystae (WCL) and soluble fraction of M. leprae sonicate (MLSA) not only inhibited TCR, thapsigargin and ionomycin induced calcium fluxes by diminishing the opening of calcium channels, but also TCR- or TCR/CD28-induced proximal signalling events like phosphorylation of Zap-70 and protein kinase-C (PKC) activity. Study of TCR- and TCR/CD28-induced downstream signals revealed that M. leprae antigens curtail phosphorylation of both Erk1/2 and p38MAPK, consequently altering terminal signalling events like reduced binding of NFAT on IL-2 promoter and transcription of IL-2 gene, diminished expression of activation markers (CD25 and CD69). Furthermore, M. leprae fractions significantly inhibited IL-2 secretion and T-cell blastogenesis in healthy

individuals. Altogether, results suggest that M. leprae interferes with TCR/CD28-induced upstream as well as downstream signalling events resulting in reduced IL-2 production and thus inhibition in T-cell proliferation, which might be responsible for T-cell unresponsiveness leading to stage of immunosuppression and consequently, for the progression of disease. (c) 2009 Elsevier Ltd. All rights reserved.

Rajashekar TS, Singh G, Naik LC. Immune zones in leprosy. Indian J Dermatol. 2009 Jul; 54(3): 206-10.

Leprosy affects mainly those areas of skin which have a relatively lower temperature and are more exposed to trauma. Certain zones like scalp, palms and soles, genitalia, groins, axillae, eyelids, transverse band of skin over lumboscaral area, midline of back and perineum have been described to be immune to the development of lesions in leprosy. But clinical, histological and bacteriological evidence of involvement of these so called immune zones though infrequent have been documented. Hence, these immune zones should be termed as relatively immune, rather than absolutely immune zones of leprosy.

Hatta M, Makino M, Ratnawati M, Mashudi M, Yadi M, Sabir M, et al . Detection of serum antibodies to M. leprae major membrane protein-II in leprosy patients from Indonesia. Lepr Rev. 2009 Dec; 80(4): 402-9.

Sero-diagnostic methods are the easiest way of diagnosing an infectious disease in developing countries. In leprosy, phenolic glycolipid-1 (PGL-I) based methods for the detection of leprosy are currently available, but the use of these methods has been hindered due to the inherent problems of sensitivity. We previously showed that antibodies to Major Membrane Protein-II (MMP-II) derived from Mycobacterium leprae could be used to diagnose leprosy in Japan. METHODS: Sera from patients and healthy individuals were collected with informed consent and the anti-MMP-II antibody levels of the sera were measured by enzyme-linked immunosorbent assay. The study was conducted at South Sulawesi and Bali, in Indonesia. The study population included 40 each of multibacillary leprosy and paucibacillary leprosy patients, 30 tuberculosis and 16 patients with typhoid. RESULTS: We evaluated the anti-MMP-II antibody levels in Indonesian individuals. The cut-off value was determined from receiver operator characteristic curve as 0.124 using the O.D. titers for patients with multibacillary leprosy, so that the sensitivity of the test was 97.5% and the specificity taking healthy individuals as controls was 984%. Using the determined cut-off values, 98% of multibacillary (MB) leprosy and 48% of paucibacillary (PB) leprosy patients had positive levels of anti-MMP-II antibodies, 13% of patients with typhoid and 22% of the household contacts of MB leprosy had positive levels of anti-MMP-II antibodies. CONCLUSIONS: Our results suggest that measuring anti-MMP-II antibody levels could facilitate the detection of leprosy in endemic countries.

Zenha EMR, Ferreira MAN, Foss NT. Use of anti-PGL-1 antibodies to monitor therapy regimes in leprosy patients. Braz. j. med. biol. res oct. 2009.

The suitability of IgM antibodies to PGL-1 for monitoring the response to multidrug therapy (MDT) was sequentially tested by ELISA in 105 leprosy patients, and bacterial indexes (BI) were also determined. Patients were divided into 3 groups: group 1, 34 multibacillary (MB) patients treated for 12 months with MDT-MB; group 2, 33 MB patients treated for 24 months with MDT-MB, and group 3, 38 paucibacillary (PB) patients treated for 6 months with MDT-PB. Untreated MB patients exhibited higher antibody levels (mean ± SEM): group 1 (6.95 ± 1.35) and group 2 (12.53 ± 2.02) than untreated PB patients (1.28 ± 0.35). There was a significant difference ($P < 0.01$) in anti-PGL-1 levels in group 1 patients: untreated (6.95 ± 1.35) and treated for 12 months (2.78 ± 0.69) and in group 2 patients: untreated (12.53 ± 2.02) and treated for 24 months (2.62 ± 0.79). There was no significant difference between untreated (1.28 ± 0.35) and treated (0.62 ± 0.12) PB patients. Antibody levels correlated with BI. The correlation coefficient (Pearson's r) was 0.72 before and 0.23 ($P < 0.05$) after treatment in group 1 and 0.67 before and 0.96 ($P < 0.05$) after treatment in group 2. BI was significantly reduced ($P < 0.01$) after 12 and 24 months on MDT

(group 1: 1.26-0.26; group 2: 1.66-0.36). Our data indicate that monitoring anti-PGL-1 levels during MDT may be a sensitive tool for evaluating treatment efficacy. These data also indicate that the control of leprosy infection can be obtained with 12 months of MDT in MB patients.

Brochado MJF, Nascimento MMP, Louzada Junior P, Figueiredo JFC, Roselino AM. Polimorfismo Val247Leu do gene β2-glicoproteína 1 pode justificar a gênese de anticorpos antiβ2GP1 e síndrome do anticorpo antifosfolípide na hanseníase multibacilar. An bras Dermatol jul.-ago. 2009; 84(4): 355-9.

FUNDAMENTOS - Anticorpos antifosfolípides (AAF), como antiβ2GP1 (β2-glicoproteína 1), são descritos na hanseníase multibacilar (MB) sem, contudo, caracterizar a síndrome do anticorpo antifosfolípide (SAF), constituída por fenômenos tromboembólicos (FTE). A mutação Val247-Leu no V domínio da β2GP1 - substituição da leucina por valina - expõe epítopos crípticos com consequente formação de anticorpos antiβ2GP1. OBJETIVO: Avaliar a associação do polimorfismo Val247Leu do gene β2GP1 com títulos de anticorpos antiβ2GP1 na hanseníase. MÉTODO: O polimorfismo Val247Leu foi detectado por PCR-RFLP, e os títulos de anticorpos antiβ2GP1, por Elisa. RESULTADOS: O genótipo Val/Val estatisticamente predominou no grupo de hansênicos, em relação ao controle. Embora maiores títulos de anticorpos antiβ2GP1 IgM estivessem alocados no grupo MB com genótipos Val/Val e Val/Leu, não houve diferença estatística em relação ao genótipo Leu/Leu. Dos sete pacientes MB com FTE, quatro apresentaram heterozigose, e três Val/Val homozigose. CONCLUSÃO: A prevalência do genótipo Val/Val no grupo de hansênicos pode justificar parcialmente a presença de anticorpos antiβ2GP1 na forma MB. A heterozigose ou homozigose Val/Val nos sete pacientes com hanseníase MB e FTE corroboram a implicação de expressão fenotípica anômala da β2GPI e formação de anticorpos antiβ2GPI, com consequente FTE e SAF.

Silva BDS, Souza MR, Kipnis TL, Junqueira-Kipnis AP. Avaliação dos anticorpos séricos totais antiglicolipídeo fenólico de Mycobacterium leprae em indivíduos portadores de hanseníase e seus contatos domiciliares no estado de Goiás, Brasil. Rev. patol. Trop jul. –set. 2009; 38(3):187-96.

A hanseníase é uma doença infecciosa, de evolução crônica, cujo agente causal é o Mycobacterium leprae, um bacilo intracelular obrigatório que infecta mais frequentemente macrófagos e células nervosas periféricas de Schwann. O diagnóstico da hanseníase é complexo, visto que a doença evolui para diferentes formas clínicas e histopatológicas. Novos testes diagnósticos têm sido propostos com o objetivo de identificar possíveis fontes de contágio e controlar a transmissão da doença. Dentre eles, destaca-se a dosagem de anticorpos IgM antiglicolipídeo fenólico (PGL-1), específico de Mycobacterium leprae, para vigilância de doentes e seus contatos. Neste trabalho, foram avaliados os níveis séricos de anticorpos totais antiPGL-1 em 102 indivíduos portadores de hanseníase (formas multibacilar e paucibaciliar) e 65 contatos domiciliares destes indivíduos, por meio de ensaio imunoenzimático. Tanto os pacientes quanto seus contatos apresentaram níveis séricos detectáveis de anticorpos antiPGL-1, o que indica potencial risco de transmissão entre eles.

Ribeiro SLE, Pereira HLA, Silva NP, Sato EI. Autoanticorpos em pacientes com hanseníase, com e sem comprometimento articular, no Estado do Amazonas. Rev. bras. Reumatol set.-out. 2009; 49(5):547-53.

OBJETIVOS: Determinar a frequência do fator reumatoide (FR-IgM), anticorpos antipeptídeos citrulinados cíclicos (anti-CCP), antinucleares (AAN), anticitoplasma de neutrófilos (ANCA), anticardiolipina (aCL) e anti-β2 glicoproteína I (anti-β2GPI) em pacientes com hanseníase, com e sem comprometimento articular, avaliando a possível associação entre estes autoanticorpos e as manifestações articulares, a forma clínica, a reação hansênica, o tratamento com poliquimioterapia (PQT) e a alta. PACIENTES E MÉTODOS: 158 pacientes com hanseníase foram distribuídos em dois grupos; 73 pacientes com

(Grupo I) e 82 sem comprometimento articular (Grupo II). Compuseram o Grupo III 129 indivíduos saudáveis. MÉTODOS: aglutinação com partículas de látex para FR-IgM, imunofluorescência indireta para AAN e ANCA, e, ELISA para anti-CCP, aCL e anti-β2GPI. RESULTADOS: Dentre 158 pacientes com hanseníase, 56 apresentavam a forma virchowiana (VV). A frequência de anticorpos anti-CCP, FR e AAN nos Grupos I e II foi semelhante à do Grupo III. ANCA não foi detectado em nenhum dos grupos. Anticorpos aCL foram mais frequentes nos pacientes com hanseníase (Grupos I e II) que em controles sadios (15,8 por cento vs. 3,1 por cento; P < 0,001), não sendo observada diferença entre Grupos I e II (P = 0,67). Anticorpos anti-β2GPI também foram mais frequentes nos pacientes que nos controles (46,2 por cento vs. 9,4; P < 0,001), sem diferença significativa entre os Grupos I e II. Houve predomínio do isotipo IgM com relação ao IgG tanto para aCL (88 por cento vs. 16 por cento, P = 0,001), quanto para anti-β2GPI (97,3 por cento vs. 12,3 por cento, P < 0,001). Nenhum paciente apresentou manifestações sugestivas de trombose vascular. CONCLUSÃO: A frequência de anticorpos aCL e anti-β2GPI foi significativamente maior nos pacientes com hanseníase que nos controles saudáveis. Entretanto, a positividade dos demais autoanticorpos foi semelhante à dos controles.

MICOBACTÉRIAS

Sekar B, Arunagiri K, Selvakumar N, Preethi KS, Menaka K. Low frequency of moaA3 gene among the clinical isolates of Mycobacterium tuberculosis from Tamil Nadu and Pondicherry--south eastern coastal states of India. BMC Infect Dis. 2009 Jul 25; 9: 114.

BACKGROUND: Comparative genomic analysis of M. tuberculosis H37Rv and M. bovis BCG have shown that 16 RDs (Regions of Differences) are deleted in BCG and have shown six deletion regions in M. tuberculosis H37Rv. RD1, is present in M. tuberculosis but is absent in all M. bovis BCG sub-strains. A study from Kerala, a south-western coastal state of India aimed to find out differences in RD1 region showed for the first time the presence of moaA3 gene in majority of their clinical isolates, that was absent in type strain H37Rv. We attempted to find out such polymorphism between type strains and the clinical isolates within RD1, targeting moaA3 gene among the clinical isolates of Tamil Nadu & Pondicherry, south-eastern coastal states of India METHODS: One hundred and sixteen clinical isolates of M. tuberculosis were included in the study. PCR using RD1DLa and RD1DRa primers was carried out to amplify a 652 bp fragment, encoding for cfp10 and esat 6 proteins of RD1. A second PCR using primers designed from the surrounding regions of moaA3 gene was done to confirm the presence of the full Open Reading Frame (ORF) in clinical isolates. RESULTS: In M. tuberculosis H37Rv the expected 652 bp band was present. In BCG it was absent as expected, but a 386 bp fragment was amplified. Around 12/116 (10.3%) of our clinical isolates showed both 652 and 386 bp fragments. The additional 386 bp amplicon is a part of the moaA3 gene which codes for molybdopterin cofactor protein A in M. bovis. The second PCR amplified the flanking sequence of moaA3 and yielded the expected amplicon of 1254 bp in all those 10.3% of clinical isolates which had the 386 bp fragment. However the earlier study carried out in Kerala, reported the presence of moaA3 gene in majority (97%) of their clinical isolates. CONCLUSION: This finding showed that there was regional variation presenting polymorphism in moA3 gene, among the strains of M. tuberculosis and further strengthens the speculation of genetic differences among the strains of Kerala and Tamil Nadu & Pondicherry, the South Indian states.

Tam PH, Lowary TL. Recent advances in mycobacterial cell wall glycan biosynthesis. Curr Opin Chem Biol. 2009 Dec; 13(5-6): 618-25.

The cell wall of mycobacteria, including the causative agents of the human diseases tuberculosis (Mycobacterium tuberculosis) and leprosy (M. leprae), is composed of an array of carbohydrate-containing molecules. These glycoconjugates are assembled by glycosyltransferases (GTs) that work in tandem through pathways that are only now beginning to be fully understood. Given the essentiality of cell wall glycans to mycobacterial viability, these enzymes represent novel targets for drug action. Summarized here are recent genetic and biochemical studies leading to the identification and characterization of mycobacterial GTs.

NEUROLOGIA / NEUROPATIA / DOR NEUROPÁTICA / NEURITE

Gondim FA, Thomas FP, Oliveira GR, Pimentel LH, Bastos BP, Costa CMC. On the spectrum of leprosy neuropathies: multifocal inflammatory neuropathy heralding leprosy relapse. Neuromuscul Disord. 2009 Oct; 19(10): 711-3.

We report a 52 year-old woman with a past history of lepromatous leprosy (14 years prior to our first evaluation) who presented with progressive weakness and severe arm/leg pain. CSF analysis revealed elevated protein level with normal cell count. Skin and sural nerve biopsy showed no bacilli. Immunomodulatory treatment led to major improvement on clinical, CSF and electrodiagnostic grounds, but after one year of treatment, skin test revealed leprosy relapse. To our knowledge, this is the first report of a multifocal inflammatory neuropathy heralding leprosy relapse. Extended neurological work-up may be important in unexplained neuropathy progression after leprosy treatment.

Smith WC, Nicholls PG, Das L, Barkataki P, Suneetha S, Suneetha L, et al. Predicting neuropathy and reactions in leprosy at diagnosis and before incident events-results from the INFIR cohort study. PLoS Negl Trop Dis. 2009 Aug 11; 3(8): e500.

BACKGROUND: Leprosy is a disease of skin and peripheral nerves. The process of nerve injury occurs gradually through the course of the disease as well as acutely in association with reactions. The INFIR (ILEP Nerve Function Impairment and Reactions) Cohort was established to identify clinically relevant neurological and immunological predictors for nerve injury and reactions. METHODOLOGY/PRINCIPAL FINDINGS: The study, in two centres in India, recruited 188 new, previously untreated patients with multi-bacillary leprosy who had no recent nerve damage. These patients underwent a series of novel blood tests and nerve function testing including motor and sensory nerve conduction, warm and cold detection thresholds, vibrometry, dynamometry, monofilament sensory testing and voluntary muscle testing at diagnosis and at monthly follow up for the first year and every second month for the second year. During the 2 year follow up a total of 74 incident events were detected. Sub-clinical changes to nerve function at diagnosis and during follow-up predicted these new nerve events. Serological assays at baseline and immediately before an event were not predictive; however, change in TNF alpha before an event was a statistically significant predictor of that event. CONCLUSIONS/SIGNIFICANCE: These findings increase our understanding of the processes of nerve damage in leprosy showing that nerve function impairment is more widespread than previously appreciated. Any nerve involvement, including sub-clinical changes, is predictive of further nerve function impairment. These new factors could be used to identify patients at high risk of developing impairment and disability.

Yamada A, Horita M, Shindo K, Ishida Y, Maeda M. Tendencies of prescriptions for neuralgic pain in National Suruga Sanatorium (leprosy), Japan during last 11 years. Nihon Hansenbyo Gakkai Zasshi. 2009 Sep; 78(3): 293-6.

The number of ex-leprosy patients has reduced rapidly who were forced to be admitted under leprosy prevention/segregation law and are staying at national sanatoriums with different disabilities due to different physical and social reasons for long time in Japan. Most of them have been of clinically cured status for decades after effective chemotherapy. Some have still been suffering from acute or chronic neuralgic pains which are supposed to be long standing consequences of nerve damage of leprosy and getting medications for long period. Pharmacy department of National Suruga Sanatorium has studied the amount of prescriptions of some medicines for last 11 years, which were thought to be prescribed for pain including neuralgic pain. There seem to be some tendencies of medications during last decade. VitaminB12 (Mecobalamine) is one of the commonest drugs for neuralgic pain at this sanatorium and the amount of prescription had almost been unchanged through the years. Prescription of non-steroid anti-inflammatory drugs (NSAIDs) increased year by year, which may reflect the increasing age of ex-patients who need more pain killers for their painful joints or back. Loxopro-

fen is the most popular pain killer here and increased by ten times for last decade. The number of prescription for Pentazocine and Hydroxyzine Hydrochloride injection increased for last several years, which reflects a few patients who were still suffering from severe chronic neuralgia for years. It is desirable that a standard regimen for chronic neuralgic pain as a consequence of nerve impairment in leprosy will be developed as soon as possible.

Guerrero-Peral AL. Neurological evaluation of the leper king Baldwin IV of Jerusalem. Rev Neurol. 2009 Oct 16-31; 49(8): 430-3.

INTRODUCTION: In the medieval period, physicians became more aware of leprosy symptoms and differentiated it from other similar diseases. Baldwin, the leper king of Jerusalem (1161-1185), probably contributed to an increasing interest and tolerance to this disease in medieval Christian states. We review historical descriptions of the neurological manifestations he developed. DEVELOPMENT: William of Tyre gives us a description of first symptoms experienced by the prince when aged nine. He notices that half of his right arm and hand were partially numb. No skin or nervous lesions are described. By his early twenties, muscle weakness makes him unable to walk. He gets blinded, probably due to keratopathy related to facial nerves involvement. Repeated attacks of fever lead to progressive worsening of his disease. He finally dies in Jerusalem, aged twenty-five, probably due to a septicaemia from infected sores. The earliest sign of Baldwin's disease is anaesthesia. Though skin lesions are not described, it is likely that at this point he had a tuberculoid form of leprosy. As his disease finally takes a lepromatous form, we suspect that it began as a borderline, immunologically unstable form. CONCLUSION: Leper king Baldwin biography gives us interesting descriptions of neurological clinical features of leprosy. Besides, it helps us to discover twelfth century medicine knowledge about this disease.

Rambukkana A. Usage of signaling in neurodegeneration and regeneration of peripheral nerves by leprosy bacteria. Prog Neurobiol. 2010 Jun; 91(2): 102-7. Epub 2009 Dec 28.

Multiple signaling pathways play key regulatory roles during the development of peripheral nervous system (PNS) and also in neuroregeneration process following nerve degeneration. Schwann cells, the glial cells of the PNS, by interacting with neuronal (axonal) ligands, mainly neuregulins via receptor tyrosine kinase (RTK) complex, ErbB2/ErbB3, initiate intracellular signaling pathways to drive proliferation and differentiation of Schwann cells, both during development and the process of regeneration and re-myelination after nerve injury. One of the major signaling kinases, extracellular signal-regulated kinase-1/2 (ERK1/2), that is also a downstream signaling pathway of neuregulin-ErbB2/ErbB3 activation, has been identified as a key regulator of Schwann cell proliferation, differentiation, demyelination and nerve regeneration. Recent studies have provided evidence that the bacterium that causes human leprosy, Mycobacterium leprae that has a unique capacity to invade Schwann cells of the adult PNS, utilizes the neuregulin-ErbB2/ErbB3 associated signaling network to the bacterial advantage. M. leprae directly bind to ErbB2 on myelinated Schwann cells and activate the RTK by a novel route that bypasses the classical neuregulin/growth factor-induced ErbB2-ErbB3 heterodimerization, and subsequently induce downstream the canonical Erk1/2 signaling, leading to myelin breakdown and subsequent axonal damage. This initial injury provides a survival advantage for M. leprae as it induces de-differentiation and generates myelin-free cells, which are highly susceptible to M. leprae invasion and promote bacterial survival. Once invaded M. leprae activate Erk1/2 via a non-canonical pathway and subsequently increase the cell proliferation and maintain the infected cells in de-differentiated state, thereby preventing remyelination. Therefore, by subverting major RTKs and signaling pathways in adult Schwann cells M. leprae appear to propagate the bacterial niche and maintain survival within the PNS. These studies may also provide new insights into our understanding of signaling mechanisms involve in both neurodegeneration and neuroregeneration.

Save MP, Shetty VP, Shetty KT. Hypophosphorylation of NF-H and NF-M subunits of neurofilaments and the associated decrease in KSPXK kinase activity in the sciatic nerves of swiss white mice inoculated in the foot pad with mycobacterium leprae. Lepr Rev. 2009 Dec; 80(4): 388-401.

To study the phosphorylation state of neurofilament (NF) proteins and activity of KSPXK kinase in the sciatic nerves of Swiss white (S/W) mice inoculated in the hind foot pads with M. leprae. DESIGN: Test group includes S/W mice inoculated in the foot pads with freshly harvested human derived (viable) M. leprae. Control groups were constituted by (1) Age matched un-inoculated mice, (2) Mice similarly inoculated with M. smegmatis and (3) heat killed M. leprae. Phosphorylation state of NF was studied using Western blot analysis and phosphor-specific NF antibody (SMI 31; Sternberger Monoclonals, Inc.). The KSPXK kinase activity was assayed by using KSPXK fusion protein in a radiometric method using gamma (22)P ATP. RESULTS: Several fold increase in M. leprae numbers was seen in viable M. leprae group while M. smegmatis failed to show any fold increase in the foot pads of S/W mice. Western immunoblot analysis of cytoskeletal preparation from sciatic nerves of uninoculated mice and mice inoculated with M. smegmatis showed immunoreactivity to SMI 31 antibody and protein bands corresponding to both NF-H and NF-M at all the time points from 4-20 months post inoculation. In case of viable M. leprae; SMI 31 reactive protein bands were seen at 4 months but not at any of the later intervals, i.e., between 6-20 months. With heat killed M. leprae transient loss of immunoreactivity to SMI 31 was seen. Decrease in KSPXK kinase activity was recorded in sets inoculated with viable and heat killed M. leprae, and corroborated with loss of immunoreactivity seen in WBs reacted with SMI 31 antibody. CONCLUSIONS: Alterations in the sciatic nerve NF cytoskeleton was seen following inoculation in the hind foot pad with both viable and heat killed M. leprae. The hypophosphorylation of NF observed in this study corroborates with the earlier observations in human leprous nerves.

Silva TH, Rodriguez OG. Neuropatía hanseniana en una adulta joven. Medisan jul.-ago. 2009; 13(4).

Se presenta el caso de una paciente de 27 años de edad, sin previos antecedentes, que en el período de puerperio comenzó a presentar deterioro neurológico progresivo, dificultad para la marcha, graves trastornos sensitivos, del tipo de las parestesias y artralgias, pérdida de la sensibilidad propioceptiva, al tacto, al dolor, a la temperatura y en zonas dístales de miembros inferiores, además de manchas violáceas en tórax, abdomen y rodillas. En la muestra para biopsia se encontró un patrón inflamatorio compatible con lepra lepromatosa.

Chacha JJ, Sotto MN, Peters L. Sistema nervoso periférico e pressupostos da agressão neural na hanseníase. An. bras. Dermatol set.-out. 2009

O mecanismo de interação entre o Mycobacterium leprae e as células neurais não está esclarecido até o momento. Não há interpretação satisfatória do tropismo da bactéria ao sistema nervoso periférico, em particular. O presente estudo é uma revisão da microfisiologia da estrutura do aparelho extracelular, ligado às células de Schwann, assim como a descrição das unidades morfológicas, provavelmente envolvidas no processo de ligação à parede celular da bactéria.

Chacha JJ, Sotto MN, Peters L, Lourenço S, Rivitti EA, Melnikov P. Peripheral nervous system and grounds for the neural insult in leprosy. An Bras Dermatol. 2009 Oct; 84(5): 495-500.

The mechanism of interaction between Mycobacterium leprae and neural cells has not been elucidated so far. No satisfactory interpretation exists as to the bacterium tropism to the peripheral nervous system in particular. The present study is a review of the micro-physiology of the extracellular apparatus attached to Schwann cells, as well as on the description of morphological units probably involved in the process of the binding to the bacterial wall

OFTALMOLOGIA

Parikh R, Thomas S, Muliyil J, Parikh S, Thomas R. Ocular manifestation in treated multibacillary Hansen's disease. Ophthalmology. 2009 Nov;116(11):2051-7.

PURPOSE: To report the prevalence of ocular morbidity in patients with treated multibacillary Hansen's disease (HD) using modern ophthalmic diagnostic techniques in a rural community endemic for HD. DESIGN: Cross-sectional, observation study. PARTICIPANTS: All patients with multibacillary HD who had completed their multidrug therapy and who resided in 4 defined geographical areas in Vellore, Tamil Nadu, India. METHODS: All participants underwent a complete eye examination that included slit-lamp examination, esthesiometry, gonioscopy, applanation tonometry, and dilated fundus examination, including a stereobiomicroscopic examination of the fundus at an ophthalmic center set up for that purpose. Glaucoma suspects underwent automated perimetry using a Humphrey Field Analyzer (Humphrey Instruments, San Leandro, CA). MAIN OUTCOME MEASURES: The prevalence of various ocular disease parameters were reported as mean value with 95% confidence interval. The difference of disease prevalence between various leprosy groups was compared using an unpaired t test. The association between eye symptoms and potentially sight-threatening complications was analyzed using the chi-square test. RESULTS: Three hundred eighty-six of the 446 patients with multibacillary HD residing in the defined areas were evaluated. Four patients (1.04%; 95% confidence interval [CI], 0.0%-2.0%) were bilaterally blind; 33 (8.55%; 95% CI, 5.8%-11.3%) had unilateral blindness. Mean intraocular pressure was 12 mmHg (standard deviation, 4.1 mmHg), and prevalence of glaucoma was 3.6% (95% CI, 1.8%-5.5%). Potentially sight-threatening (PST) pathologic features (corneal anesthesia, lagophthalmos, uveitis, scleritis, and advanced glaucoma) were present in 10.4% (95% CI, 7.4%-13.4%) of patients. Significant cataracts occurred 3 times more frequently in those with polar lepromatous leprosy. The odds ratio for PST pathology in the presence of patient-reported symptoms (pain, redness, inability to close eye, burning, and irritation) was 2.9 (95% CI, 1.34-6.26). CONCLUSIONS: Patients who have completed treatment for multibacillary HD continue to have significant ocular morbidity. A history of specific eye symptoms can be the basis for referral by field staff.

Cohen JM. Ocular leprosy: a historical approach. Arq Bras Oftalmol. 2009 Sep-Oct; 72(5): 728-33.

A sharp drop in the prevalence of leprosy occurred in the last three decades. However, the incidence has not decreased at the same rate. Three years after the World Health Organization last deadline for leprosy control, patients considered healed still need special care for their incapacities and immunopathological reactions. Medical literature reffers blindness in 4% to 11% of studied patients and more than 20% with severe visual problems due to corneal exposure, bacillary invasion and hipersensibility. These mechanisms result in a population of nearly one million blind leprosy patients even though official prevalence accounts no more than 250,000 patients worldwide. The author calls for better patients management and follow-up and urges ophthalmologists to become more aware and interested in the treatment of the ocular complications of leprosy.

Cohen JM. Hanseníase ocular: uma abordagem histórica. Arq. bras. Oftalmol set.-out. 2009; 72(5):728-33.

Houve uma acentuada queda na prevalência da hanseníase nas últimas três décadas. Contudo, a incidência não diminuiu na mesma proporção. Hoje, três anos após a última data estipulada pela Organização Mundial da Saúde para o controle da hanseníase, pacientes considerados curados ainda necessitam de cuidados especiais por causa de suas incapacidades e reações imunológicas. A literatura médica refere cegueira em 4 por cento a 11 por cento dos pacientes estudados e, mais de 20 por cento com graves problemas visuais devido a exposição da córnea, invasão bacilar e hipersensibilidade; estes mecanismos resultam em uma população de aproximadamente 1 milhão de pacientes cegos, embora a prevalência oficial não passe de 250.000 pacientes em todo o mundo. O autor destaca a necessidade de melhor tratamento e acompanhamento dos pacientes e, conclama os oftalmologistas a tornarem-se mais perceptivos e se interessarem mais pelo tratamento das complicações oculares da hanseníase.

PATOLOGIA / HISTOPATOLOGIA

Quaresma JAS, Oliveira MF, Guimarães ACR, Brito EB, Pagliari C, Brito AC, et al. CD1a and factor XIIIa immunohistochemistry in leprosy: a possible role of dendritic cells in the pathogenesis of Mycobacterium leprae infection. Am J Dermatopathol. 2009 Aug; 31(6): 527-31.

Leprosy is a curable chronic granulomatous infectious disease caused by the bacillus Mycobacterium leprae. This organism has a high affinity for skin and peripheral nerve cells. In the evolution of infections, the immune status of patients determines the disease expression. Dendritic cells are antigen-presenting cells that phagocytose particles and microorganisms. In skin, dendritic cells are represented by epidermal Langerhans cells and dermal dendrocytes, which can be identified by expression of CD1a and factor XIIIa (FXIIIa). In the present study, 29 skin samples from patients with tuberculoid (13 biopsies) and lepromatous (16 biopsies) leprosy were analyzed by immunohistochemistry using antibodies to CD1a and FXIIIa. Quantitative analysis of labeling pattern showed a clear predominance of dendritic cells in tuberculoid leprosy. Difference between the number of positive cells of immunohistochemistry for the CD1a and FXIIIa staining observed in this study indicates a role for dendritic cells in the cutaneous response to leprosy. Dendritic cells may be a determinant of the course and clinical expression of the disease.

Rashed HA, Mearag I, Saleh NM, Saied A. Histopathological lesions of apparently normal skin in leprosy patients. J Egypt Soc Parasitol. 2009 Dec; 39(3): 933-42.

This study was carried out on 50 patients with different clinical types of leprosy 38 males (76 % and 12 females (24%), ages ranged from 14 -70 years with a mean age +/- SD 49.22 +/- 12.97 years. Mean disease duration was 5.65 years +/- SD = 9.27 selected to study a group of leprosy patients and compare the clinical parameters with histopathological findings and bacteriologic status of the skin to evaluate the relevance of their patients. Patients were subjected to full medical history taking including disease duration, type and duration of previous or current therapies. Complete clinical examination, for the determination of the clinical type of leprosy. Skin slit smear (SSS) and skin biopsies were taken and examined after staining for histopathological assessment and Acid fast bacilli (AFB). SPSS package version (statistical Package for Social Sciences) was used for data analysis. The biopsy of normally looking skin showed classic histopathological features of leprosy in more than half of the cases (26 cases, 52%). The histopathological types of leprosy diagnosed in such cases were as follows: indeterminate leprosy (IL) in 4 cases (15.38%), Tuberculoid leprosy (TL) in 2 cases (7.69%), Borderline tuberculoid (BT) in 4 cases (15.38), Borderline Borderline (BB) i.e Query in 8 cases (30.76%), Borderline Lepromatous (BL) in 7 cases (26.92%) and Lepromatous leprosy (LL) in a patient (3.84%). Other 24 cases showed either no evidence of leprosy in (9 cases, 37.5%), or query findings (in the form of sweat gland changes either alone or in combination with thickened nerves and superficial and deep perivascular lymphohistiocytic infiltrate) in 15 cases (62.5%). Histopathology of skin lesion biopsies showed TL in 3 cases (6%), BT in 8 cases (16%), BB in 8 cases (16%), BL in 14 cases (28%), LL in 12 cases (24%) and leprosy in reaction in 5 cases (10%). In 16 cases (32%), histopathological type of leprosy detected by microscopical examination of biopsies from skin lesions differed from that diagnosed by clinical examination.

PREVENÇÃO

Schuring RP, Richardus JH, Pahan D, Oskam L. Protective effect of the combination BCG vaccination and rifampicin prophylaxis in leprosy prevention. Vaccine. 2009 Nov 23; 27(50): 7125-8.

BCG vaccination and rifampicin chemoprophylaxis are both strategies for leprosy prevention. While the combined effect is unknown, the combination may give the desired push to halt leprosy transmission. Secondary analysis was done on results from a single centre, double blind, cluster randomized, and placebo-controlled trial. Individually, BCG (given at infancy) and rifampicin showed to protect against leprosy (57% [95% CI: 24-75%] and 58% [95% CI: 30-74%], respectively). The combined strategies showed a protective effect of 80% (95% CI: 50-92%). This is the first time that the additive effect of BCG and rifampicin are shown; the combined strategies can possibly lower leprosy incidence

Reveiz L, Buendía JA, Téllez D. Chemoprophylaxis in contacts of patients with leprosy: systematic review and meta-analysis. Rev. panam. salud pública oct. 2009; 26(4): 341-9.

OBJECTIVE: To identify and summarize randomized clinical trials (RCTs) that assessed the effectiveness of chemoprophylaxis to prevent leprosy in contacts of patients newly diagnosed with the disease. METHODS: All studies were extracted from Medline (PubMed 1966 to November 2008), the Cochrane Controlled Trials Register (number 3 2008), LILACS (1982 to November 2008), and Scirus (November 2008). Manual searches and searches of crossed references of assessed articles were also done. RCTs' risk of bias was assessed according to the methodology proposed by the Cochrane Collaboration. The main outcome measure was diagnosis of leprosy (secondary cases) in contacts of patients with the disease (primary cases). RESULTS: The search identified 320 references, from which 7 RCTs with a total of 66 311 participants were included and evaluated. The combined results from the RCTs favored chemoprophylaxis to placebo with 2-4 years of follow-up (6 RCTs, 66 107 participants, relative risk (RR) 0.59, 95 percent confidence interval (CI) 0.50-0.70, $I^2 = 0$ (I^2 describes percent total variation across studies caused by heterogeneity)). Single-dose rifampicin (21 711 participants, RR 0.43, 95 percent CI 0.28-0.67, number needed to treat 285), dapsone once or twice weekly for at least 2 years (3 RCTs, 43 137 participants, RR 0.60, 95 percent CI 0.48-0.76, $I^2 = 0$), and acedapsone every 10 weeks for 7 months (2 RCTs, 1 259 participants, RR 0.49, 95 percent CI 0.33-0.72, $I^2 = 0$) were significantly superior to placebo in preventing secondary cases of leprosy. CONCLUSION: Chemoprophylaxis is effective in lowering the incidence of leprosy in contacts of patients diagnosed with the disease.

PSIQUIATRIA

Erinfolami AR, Adeyemi JD. A case control study of psychiatric morbidities among subjects with leprosy in Lagos, Nigeria. Int J Psychiatry Med. 2009; 39(1): 89-99.

OBJECTIVES: To determine the pattern of psychiatric morbidity prevalent among leprosy patients and to compare it with two control groups; those suffering from Tinea vesicolor and Normal subjects. DESIGN: Eighty-eight leprosy patients were matched for age and sex with those suffering from Tinea vesicolor as well as normal subjects. The subjects were assessed for psychiatric morbidity through a clinical interview with PSE-9. RESULTS: The prevalence of psychiatric morbidity among leprosy patients (580/1000) was significantly more than those with tinea vesicolor patients (182/1000) and normal subjects (148/1000) ($p < 0.05$). Depressive illness was the most common diagnosis in the three groups. CONCLUSIONS: Leprosy patients are more likely to manifest with psychiatric illness than those suffering from Tinea vesicolor and normal subjects.

QUALIDADE DE VIDA

An JG, Ma JH, Xiao SX, Xiao SB, Yang F. Quality of life in patients with lepromatous leprosy in China. J Eur Acad Dermatol Venereol. 2009 Dec 15

Abstract Background Leprosy has an impact on patients' quality of life (QoL). However, there has been no study specifically on the impact of the severest type of leprosy-lepromatous leprosy on QoL. Objective To describe the use of Dermatology Life Quality Index (DLQI) among patients with lepromatous leprosy in China. Methods Sixty-four inpatients with lepromatous leprosy of Shangluo hospital and Hanzhong hospital and sixty-four controls (healthy volunteers or patients with other dermatoses) matched for age and gender were asked to complete DLQI questionnaires from 2 September 2008 to 20 December 2008. Extensive data were collected besides DLQI, including demographic data and disease-related characteristics. Absence or presence of disability among patients with lepromatous leprosy was evaluated at the same time. Results The overall mean DLQI score for lepromatous leprosy (18.78) was higher than that for control (9.00) ($P < 0.001$). Patients with lepromatous leprosy scored significantly higher for all items ($P < 0.001$) except Q4 (clothes choice). Controls scored significantly lower for all domains of DLQI. Scores of LL increased markedly with increasing clinical severity, but were not associated with educational level, gender, age and disease duration. The inter-item correlation averaged 0.240 and Cronbach's

alpha was 0.759, indicating high internal consistency. Conclusions This is the first exclusive study to attempt to measure the impact of lepromatous leprosy on QoL. Lepromatous leprosy has a severe impact on QoL.

REAÇÕES ADVERSAS À PQT / TALIDOMIDA / ESTERÓIDES

Fabi SG, Hill C, Witherspoon JN, Boone SL, West DP. Frequency of thromboembolic events associated with thalidomide in the non-cancer setting: a case report and review of the literature. J Drugs Dermatol. 2009 Aug; 8(8): 765-9.

Thalidomide is increasingly being used due to its effectiveness in the treatment of a variety of dermatologic conditions refractory to other treatments. Although thalidomide's side effects have been well-documented in the literature since its entry in the 1950s, some of the risks associated with its use are still being discovered. Recently, increased incidence of venous thrombosis following thalidomide use has been reported in the treatment of diseases with disease-related thrombotic risks, such as malignancy and lupus with antiphospholipid antibody syndrome, as well as concomitant therapy with chemotherapy and/or systemic corticosteroids. We report a case of deep venous thrombosis (DVT) and pulmonary embolus (PE) following thalidomide use in a patient with leprosy (erythema nodosum leprosum, ENL) who was concurrently treated with prednisone, as well as a review of relevant literature. Our findings substantiate an increase in risk for thrombosis following thalidomide use in the dermatology and non-cancer clinical setting.

Chun JS, Yun SJ, Kim SJ, Lee SC, Won YH, Lee JB. Dapsone hypersensitivity syndrome with circulating 190-kDa and 230-kDa autoantibodies. Clin Exp Dermatol. 2009 Dec; 34(8): e798-801.

Dapsone has potent anti-inflammatory effects, and is used in the treatment of leprosy, cutaneous vasculitis, neutrophilic dermatoses, and dermatitis herpetiformis and other blistering disorders. However, it may cause severe adverse reactions such as hypersensitivity syndrome, which is characterized by fever, skin rash, hepatitis and lymphadenopathy. We report a 44-year-old female Korean patient with dapsone hypersensitivity syndrome (DHS) that presented as a bullous skin eruption. The patient had a 1-year history of urticarial vasculitis, treated with antihistamines, prednisolone and dapsone. Although the skin lesions improved, she reported fever, nausea, abdominal pain, jaundice, fatigue and skin rashes. On physical examination, there were generalized erythematous macules and purpura with facial oedema that developed into vesicles on the upper limbs. Histological examination of a skin biopsy of a vesicular lesion found subepidermal oedema with a mixed inflammatory cell infiltrate, including eosinophils in the dermis. Indirect immunofluorescence testing using normal foreskin as substrate revealed IgG deposits in the basement membrane zone. Circulating autoantibodies against antigens of 190 and 230 kDa were found by immunoblotting analysis using epidermal extracts. This case illustrates DHS with the formation of circulating autoantibodies.

Papang R, John AS, Abraham S, Rao PS. A study of steroid-induced diabetes mellitus in leprosy. Indian J Lepr. 2009 Jul-Sep; 81(3): 125-9.

Steroids, while still the most powerful drugs to manage leprosy reactions, predispose some patients to other morbidities such as diabetes, glaucoma, hypertension etc. A prospective cohort study was done in Kolkata, India among leprosy patients in reaction to determine the extent of steroid induced diabetes mellitus (SID). All leprosy patients with type 1 or type 2 reactions or neuritis admitted in 2006 to the Leprosy Mission Hospital in Kolkata, who had no past or current history and whose blood sugars on fasting were <126 mg/dl or postprandial <200 mg/dl were monitored fortnightly while on steroid therapy, estimating blood glucose by a glucometer using standard strips. Of 81 patients, 19 (23.5%) manifested steroid-induced diabetes mellitus. Compared to those who didn't, there were significantly more LL/BL patients with positive BI among SID whose cumulative prednisolone dosage was nearly 9000 mg as compared to half the amount among others. Steroid induced diabetes is a serious complication among leprosy patients treated with

prednisolone for reactions requiring careful monitoring for detection and appropriate clinical management.

RECIDIVA / REATIVAÇÃO / RESISTÊNCIA A PQT

Fajardo TT, Villahermosa L, Pardillo FE, Abalos RM, Burgos J, Cruz ED, et al. A comparative clinical trial in multibacillary leprosy with long-term relapse rates of four different multidrug regimens. Am J Trop Med Hyg. 2009 Aug; 81(2): 330-4.

As a participant in a multicenter trial, we evaluated the relapse rate in 189 multibacillary (MB) leprosy patients treated with four different regimens and followed-up for as many as 12 years after the initiation of treatment. Treatment regimens included 1 year of WHO MDT (a regimen including dapsone, clofazimine, and rifampin), 2 years of WHO MDT, 1 month of daily rifampin and daily ofloxacin, and 1 year of WHO MDT plus an initial 1 month of daily rifampin and daily ofloxacin. Relapse rates after 9 and 12 years from the initiation of therapy in the three regimens that included WHO MDT were 0-3%, whereas relapses occurred in those treated with the 1-month regimen alone at a significantly greater rate ($P < 0.05$): 11% at 9 years and 25% at 12 years. Relapses occurred late, beginning at 5 years after the initiation of therapy, and were confined to those patients histopathologically borderline lepromatous and polar lepromatous having a high bacterial burden. Prospects for an alternative effective short-course therapy of leprosy are presented.

Diniz LM, Moreira MV, Puppin MA, de Oliveira ML. Retrospective study on leprosy relapse in the State of Espírito Santo. Rev Soc Bras Med Trop. 2009 Jul-Aug; 42(4): 420-4.

Leprosy relapse is the reappearance of the disease after regular treatment with current regimens and discharge due to cure. In this retrospective and descriptive cohort study, the aim was to evaluate the characteristics of cases of leprosy relapse in the State of Espírito Santo between 2000 and 2005. The investigation strategies consisted of monitoring the SINAN entries, with file analysis and case discussions at the State Reference Center. One hundred and four cases of relapse were studied, representing 1.12% of the new cases detected over this period. The greatest frequency was between 21 and 60 years of age; 59.6% were men; 44.2% presented relapse more than five years after discharge; 66.4% were multibacillary; and 42.2% presented positive bacilloscopy (complete bacilli) and therefore were relapse cases. Negatives bacilloscopy was observed in 57.8%. Prospective studies should be conducted to establish the real relapse rate.

Balagon MF, Cellona RV, Cruz E, Burgos JA, Abalos RM, Walsh GP, et al. Long-term relapse risk of multibacillary leprosy after completion of 2 years of multiple drug therapy (WHO-MDT) in Cebu, Philippines. Am J Trop Med Hyg. 2009 Nov; 81(5): 895-9.

From 1987 to 1994, we enrolled 500 subjects completing 2-year WHO multiple drug therapy (MDT) for multibacillary leprosy in a prospective relapse study. Relapse was defined as new skin lesions and an increase in the bacterial index (BI) > or = 2+ (> or = 100x) at any single slit-skin smear site. At the study end in 2006, follow-up was 6,401 subject-years, a mean of 12.8 years/subject. We observed 23 relapses, 6-16 years after MDT (mean, 10.5 years; 95% confidence interval [CI], 9.2-11.8), peaking in Years 11-12 (> 1%/year). The cumulative risk was 6.6% (95% CI, 5.0-8.2%). In a subset of 181 subjects with pre-MDT average BI > or = 4+, 11 relapses occurred (cumulative risk, 10.1%). In mouse footpad assays, Mycobacterium leprae from relapsed subjects were rifampin and clofazimine sensitive. Taken together, the data suggest relapses are related to activation of dormant organisms (persisters) not killed by MDT rather than new infection.

Joshi PL, Thorat DM, Manglani PR. Need and strategy for sentinel surveillance for drug resistance in leprosy in India. Indian J Lepr. 2009 Jul-Sep; 81(3): 113-8.

In the fight against leprosy drug resistance poses a serious impediment at a stage when there is dramatic decline in prevalence due to intensive and concerted chemotherapy intervention. Drug resistance in leprosy has been reported since 1964 for dapsone, 1976 for rifampicin and 1996 for ofloxacin. Recent reports and

publications have indicated few instances of rifampicin resistance in several endemic areas. In light of reporting drug resistance in leprosy, the National Leprosy Eradication Programme (NLEP) in India has started collecting information on relapse cases from peripheral institutions. The data show quite significant number of relapse cases (328 in year 2008-09) reported from few endemic states. Comprehensive data on the magnitude of drug resistance are crucial to evaluate the efficacy of MDT and to maintain the effectiveness of the current leprosy control strategy. It has become a necessity to develop a surveillance system to keep a close vigil on drug resistance. PCR based assays have convincingly demonstrated that detection of rifampicin resistance by this method is a feasible and practical alternative to the mouse foot pad (MFP) assay and has practical application in India. Surveillance of drug resistance in leprosy can be carried out based on a sentinel surveillance model. Certain district hospitals and tertiary institutions can be identified as sentinel sites in endemic states where tissue samples can be collected and transported to the identified reference laboratories. Based on the suspected and confirmed relapsed cases reported, 12 states have been identified for inclusion under the surveillance of drug resistance in leprosy. These are Andhra Pradesh, Bihar, Chhattisgarh, Karnataka, Madhya Pradesh, Maharashtra, Orissa, Rajasthan, Tamilnadu, Uttar Pradesh, West Bengal and Delhi. Four reference laboratories have already been identified, one each in the states of Uttar Pradesh, Andhra Pradesh, Tamilnadu and Delhi. Tissue samples from sentinel sites would be sent to designated laboratories for conducting the DNA sequencing tests to confirm rifampicin resistance.

Gupta UD, Katoch K, Katoch VM. Study of rifampicin resistance and comparison of dapsone resistance of M. leprae in pre- and post-MDT era. Indian J Lepr. 2009 Jul-Sep; 81(3): 131-4.

The aim of this study to study the drug resistance patterns of dapsone (pre- and post-MDT) and rifampicin (post-MDT era). All the 84 patients from pre-MDT period (1985-1990) and 77 patients for post-MDT period (1990-2002) reporting to a tertiary care hospital-NJIL & OMD, Agra and referred for drug susceptibility testing were included in the study. Drug resistance was studied by mouse foot pad method. Dapsone resistance was high during pre-MDT era i.e. 8.3% (medium) and 19.1% (high) with an overall dapsone resistance of 27.4%. During the post-MDT era, the dapsone resistance was low i.e. 1.3% (medium) and 3.9% (high) respectively (overall dapsone resistance-5.2%). While no comparison with pre-MDT era is available, the rifampicin resistance in these selected self-reporting cases during the post-MDT era was comparatively rather high (9.1%). MDT appears to have been useful in reducing the prevalence of dapsone resistance in leprosy patients reporting to a tertiary care hospital.

Diniz LM, Moreira MV, Puppin MA, Oliveira MLWDR. Estudo retrospectivo de recidiva da hanseníase no Estado do Espírito Santo. Rev. Soc. Bras. Med. Trop jul-ago. 2009; 42(4): 420-4.

Recidiva de hanseníase é o reaparecimento da doença, após tratamento regular com os esquemas vigentes e alta por cura. Neste estudo de coorte retrospectivo e descritivo o objetivo foi avaliar as características dos casos de recidiva de hanseníase no Estado do Espírito Santo entre 2000 e 2005. As estratégias de investigação foram: monitoramento das entradas no SINAN, análise das fichas e discussão dos casos no Centro de Referência Estadual. Foram estudados 104 casos de recidiva, representando 1,12 por cento em relação aos casos novos diagnosticados no período. A maior freqüência foi entre 21 a 60 anos; 59,6 por cento eram do sexo masculino; 44,2 por cento apresentaram a recidiva após cinco anos da alta; 66,4 por cento eram multibacilares, sendo 42,2 por cento com baciloscopias positivas (bacilos íntegros), portanto recidivas. Baciloscopias negativas foram observadas em 57,8 por cento. Estudos prospectivos devem ser feitos para estabelecimento da taxa real de recidiva.

SAÚDE PÚBLICA

Imbiriba EN, Silva Neto AL, Souza WV, Pedrosa V, Cunha MG, Garnelo L. Social inequality, urban growth and leprosy in Manaus: a spatial approach. Rev Saude Publica. 2009 Aug; 43(4): 656-65.

OBJECTIVE: To analyze the epidemiology of leprosy according to spatial distribution and living conditions of the population. METHODS: Ecological study based on the spatial distribution of leprosy in the municipality of Manaus, Northern Brazil, from 1998 to 2004. The 4,104 cases identified in the Sistema de Informações de Agravos de Notificação (Sinan -National Notification System) were georeferenced according to the addresses in the 1,536 urban census tracts through four different sources: postal service (73.7% of addresses found), Property Registration Program (7.3%), Family Health Program (2.1%), and Instituto Brasileiro de Geografia e Estatística (Brazilian Institute of Geography and Statistics) data sheet (1.5%). Calculation of detection coefficient was performed based on the 2001 population. Local empirical Bayesian method was used for the spatial distribution analysis, in order to estimate leprosy risk, making rate variation shorter when they were calculated for small areas. Logistic regression was employed to analyze the association between geographical distribution and risk factors. The incidence of cases in children under 15 (severity indicator) and Social Need Index built from variables of the 2000 census were adopted as explicative variables. RESULTS: The mean coefficient of detection was hyperendemic in 34.0% of the census tracts, and very high in 26.7%. Odds ratio was obtained for explicative variables and proved to be significant. Low-income and incidence in children under 15 were combined to identify priority areas for intervention. CONCLUSIONS: Spatial analysis of leprosy showed that the distribution of the disease is heterogeneous and is more strongly present in regions inhabited by more vulnerable groups.

Feasey N, Wansbrough-Jones M, Mabey DC, Solomon AW. Neglected tropical diseases. Br Med Bull. 2010; 93: 179-200.

INTRODUCTION: The neglected tropical diseases (NTDs) are infectious diseases that principally impact the world's poorest people. They have been neglected for decades, initially as part of a general disregard for the developing world, and more recently due to the intensity of focus on HIV/AIDS, tuberculosis and malaria. SOURCES OF DATA: Primary research and review articles were selected for inclusion using searches of PubMed and our existing collections. RESULTS: There have been recent notable successes in NTD control. Dracunculiasis is approaching eradication. Leprosy and onchocerciasis are in decline. There are ambitious plans to eliminate trachoma and lymphatic filariasis. Investment in NTD control has high rates of economic return. CONCLUSION: Although there are proven strategies to control several NTDs, these diseases continue to cause a massive burden of morbidity. There is urgent need for more basic and operational research, drug and vaccine development, and greater prioritization by governments and international agencies.

TERAPÊUTICA

Van Veen NH, Lockwood DN, van Brakel WH, Ramirez JJ, Richardus JH. Interventions for erythema nodosum leprosum. Cochrane Database Syst Rev. 2009 Jul 8; (3): CD006949.

BACKGROUND: Erythema nodosum leprosum (ENL) is a serious immunological complication of leprosy, causing inflammation of skin, nerves, other organs, and general malaise. Many different therapies exist for ENL, but it is unclear if they work or which therapy is optimal. OBJECTIVES: To assess the effects of interventions for erythema nodosum leprosum. SEARCH STRATEGY: We searched the Cochrane Skin Group Specialised Register, the Cochrane Central Register of Controlled Trials (CENTRAL) in The Cochrane Library (Issue 1, 2009), MEDLINE (from 2003), EMBASE (from 2005), LILACS and AMED (from inception), CINAHL (from 1981), and databases of ongoing trials, all in March 2009. We checked reference lists of articles and contacted the American Leprosy Missions in Brazil to locate studies. SELECTION CRITERIA: Randomised controlled trials (RCTs) of interventions for ENL in people with leprosy. DATA COLLECTION AND ANALYSIS: Two authors performed study selection, assessed trial quality, and extracted data. MAIN RESULTS: We included 13 studies with a total of 445 participants. The quality of the trials

was generally poor and no results could be pooled due to the treatments being so heterogeneous. Treatment with thalidomide showed a significant remission of skin lesions compared to acetylsalicylic acid (aspirin) (RR 2.43; 95% CI 1.28 to 4.59) (1 trial, 92 participants). Clofazimine treatment was superior to prednisolone (more treatment successes; RR 3.67; 95% CI 1.36 to 9.91) (1 trial, 24 participants), and thalidomide (fewer recurrences; RR 0.08; 95% CI 0.01 to 0.56) (1 trial, 72 participants). We did not find any significant benefit for intravenous betamethasone compared to dextrose (1 trial, 10 participants), pentoxifylline compared to thalidomide (1 trial, 44 participants), indomethacin compared to prednisolone, aspirin or chloroquine treatments (2 trials, 80 participants), or levamisole compared to placebo (1 trial, 12 participants). Mild to moderate adverse events were significantly lower in participants taking 100 mg thalidomide compared to 300 mg thalidomide daily (RR 0.46; 95% CI 0.23 to 0.93). Significantly more minor adverse events were reported in participants taking clofazimine compared with prednisolone (RR 1.92; 95% CI 1.10 to 3.35). None of the studies assessed quality of life or economic outcomes. AUTHORS' CONCLUSIONS: There is some evidence of benefit for thalidomide and clofazimine, but generally we did not find clear evidence of benefit for interventions in the management of ENL. However, this does not mean they do not work, because the studies were small and poorly reported. Larger studies using clearly defined participants, outcome measures, and internationally recognised scales are urgently required

Kaur I, Dogra S, Narang T, De D. Comparative efficacy of thalidomide and prednisolone in the treatment of moderate to severe erythema nodosum leprosum: a randomized study. Australas J Dermatol. 2009 Nov; 50(4): 307

The present study was undertaken to compare the efficacy and safety of thalidomide to that of oral prednisolone in the treatment of moderate to severe type 2 lepra reaction. Sixty patients with a histologically confirmed diagnosis of erythema nodosum leprosum with a clinical score of 4 or more (i.e. moderate to severe type 2 reaction) were randomly allocated to two groups comprising 30 patients each. Group 1 patients were given thalidomide at a dose of 300 mg/day for 1 week and the dose was gradually reduced, and Group 2 received prednisolone 40 mg daily for 2 weeks, which was tapered by 10 mg every 2 weeks. Thalidomide induced a faster clinical response (cutaneous as well as systemic) compared with prednisolone. Patients taking thalidomide had fewer relapses and a longer period of remission than those receiving prednisolone.

Vieira JL, Valente MS. Thalidomide levels in patients with erythema nodosum leprosum. Ther Drug Monit. 2009 Oct; 31(5): 602-3.

Thalidomide is used for the acute treatment and suppression of the cutaneous manifestations of erythema nodosum leprosum (ENL). In this study, comparisons were made regarding the plasma concentrations of thalidomide in patients with ENL on the course or after leprosy therapy in a prospective clinical trial. Thalidomide concentrations were measured by liquid chromatography on days 1, 3, and 14 of treatment. After 100 mg/d, the thalidomide concentrations ranged from 0.82 to 1.03 and 0.43 to 0.80 microg/mL, on the course or after leprosy therapy, respectively. No differences were observed in thalidomide concentrations between and within the groups. Our results suggested that leprosy multidrug therapy does not seem to affect the plasma concentrations of thalidomide in patients with ENL.

Safa G, Darrieux L, Coic A, Tisseau L. Type 1 leprosy reversal reaction treated with topical tacrolimus along with systemic corticosteroids. Indian J Med Sci. 2009 Aug; 63(8): 359-62.

An 11-year-old black Haitian boy presented with borderline lepromatous leprosy and was treated with rifampicin, dapsone, and clofazimine. After 4 months he developed a severe type 1 reversal reaction without nerve involvement. He was started on prednisolone (1 mg/kg daily). After 4 weeks of treatment with corticosteroids, his condition did not improve and the lesions remained painful. The patient was given a therapeutic trial with

twice daily application of topical tacrolimus 0.1% ointment. The result was a dramatic improvement in the skin lesions. The patient's condition was maintained by topical tacrolimus therapy, with healing of all skin lesions. The prednisolone dose was then tapered to zero over a period of 12 weeks. To the best of our knowledge, this is the first report of the efficacy of topical tacrolimus in the treatment of type 1 leprosy reaction.

Ishida Y. Prevalence of disability among leprosy patients and effectiveness of leprosy reaction services with standard prednisolone treatment at field level in an endemic country--some data from joint leprosy research collaboration in Myanmar. Nihon Hansenbyo Gakkai Zasshi. 2009 Sep; 78(3): 277-82.

Prevalence of disability among leprosy patients and effectiveness of standard predonisolone treatment for leprosy reaction at field level in some place of Myanmar are shown in this paper as results of joint leprosy research collaboration. WHO disability grading was measured for all newly registered leprosy patients through 2007 in 5 selected townships of Ayeyarwaddy Division, with the results of G0 = 66.3%, GI = 18.9%, GII = 14.7% (N = 95). The cross-sectional disability survey at selected 9 townships in Mandalay, Sagaing and Magway Division for all registered patients who had completed WHO/MDT done by JICA project in 2003/4 showed G0 = 62.5%, GI = 2.4%, GII = 35.1% (N = 10,528). From these two data, it is supposed that considerable number of patients with G1 at registered time developed worsening of disability from G1 to G2. Proportion of G0 also reduced a little bit in patients who completed WHO/MDT. Early detection and proper treatment of leprosy reaction are one of the main issues of prevention of disability. Effectiveness of leprosy reaction services were evaluated at Mandalay Special Skin Clinic, where WHO fixed regimen of prednisolone were given as routine service. 100 cases were evaluated who developed leprosy reactions from 1st December 2007 to 31st December 2008 and identified severe reaction who needed oral prednisolone treatment. Evaluation criteria of "effective" was defined as "no more signs and symptoms of reactions were present after treatment. And "less effective" was defined as "more than one of signs and symptoms were still remained after treatment". Over all "effective" was 36 (36%) and "less effective" was 64 (64%). It was also found that rates of improvement of nerve functions, either in sensory or in motor, were little after the standard treatment.

Gautam VP. Treatment of leprosy in India. J Postgrad Med. 2009 Jul-Sep; 55(3): 220-4.

Introduction of multi-drug therapy (MDT) into the National Leprosy Eradication Program (NLEP) of India has brought a decline in both the burden of the disease and the detection of new cases in the country. Despite this success, MDT has had many problems like remarkable relapse rate, non-adherence to the MDT and the emergence of drug resistance associated with it. Moreover, there is no new MDT regimen at present, which could solve all these problems. The current situation suggests that we should look for alternative solutions in the delivery of leprosy-related services. With the introduction of Accredited Social Health Activists under the National Rural Health Mission, there is an opportunity to control some of these problems associated with MDT. Besides, District Nucleus should take initiatives and actively participate in establishment of coordination between departments of Health, Social welfare and justice, education and various non-governmental agencies working in the field of leprosy and disability in order to deliver the best of services to the persons affected by leprosy.

Worobec SM. Treatment of leprosy/Hansen's disease in the early 21st century. Dermatol Ther. 2009 Nov-Dec; 22(6): 518-37.

Leprosy, or Hansen's disease (HD), is caused by Mycobacterium leprae, a slowly dividing mycobacterium that has evolved to be an intracellular parasite, causing skin lesions and nerve damage. Less than 5% of people exposed to M. leprae develop clinical disease. Host cell-mediated resistance determines whether an individual will develop paucibacillary or multibacillary disease. Hansen's disease is a worldwide disease with about 150 new cases reported annually in the United States. Ef-

fective anti-mycobacterial treatments are available, and many patients experience severe reversal and erythema nodosum leprosum reactions that also require treatment. Leprosy has been the target of a World Health Organization multiple drug therapy campaign to eliminate it as a national public health problem in member countries, but endemic regions persist. In the United States, the National Hansen's Disease Program has primary responsibility for medical care, research, and information.

Van Veen NH, Lockwood DN, Van Brakel WH, Ramirez J, Richardus JH. Interventions for erythema nodosum leprosum. A Cochrane review. Lepr Rev. 2009 Dec; 80(4): 355-72

Treatment for erythema nodosum leprosum (ENL), an immunological complication of leprosy, is diverse. We undertook a systematic review as it was not clear which treatments were most beneficial. METHODS: We did a systematic search to identify randomised controlled trials (RCTs) comparing treatment with placebo, no treatment or another therapy. Two authors assessed quality and checked data. RESULTS: We included 13 studies involving 445 participants. These trials assessed: betamethasone, thalidomide, pentoxifylline, clofazimine, indomethacin and levamisole. The quality of the trials was generally poor and no results could be pooled due to the treatments being so heterogeneous. Treatment with thalidomide showed a significant benefit compared to aspirin (RR 2.43; 95% CI 1.28 to 4.59). Clofazimine treatment was superior to prednisolone (more treatment successes; RR 3.67; 95% CI 136 to 9.91) and thalidomide (fewer recurrences; RR 0.08; 95% CI 0.01, 0-56). Minor adverse events were significantly lower in participants on a low dose thalidomide regimen compared to a high dose thalidomide regimen (RR 0.46; 95% CI 0.23 to 0.93). Significantly more minor adverse events were reported in participants taking clofazimine compared with prednisolone (RR 1.92; 95% CI 1.10 to 3.35). None of the studies assessed quality of life or economic outcomes. CONCLUSION: There is some evidence of benefit for thalidomide and clofazimine, but generally we did not find clear benefits for interventions in the management of ENL. This does not mean they do not work because the studies were small and poorly reported. Larger studies using clear definitions and internationally recognised scales are urgently required.

TRANSMISSÃO

Aguas JT. Infectious nature of leprosy, by Juan de Azúa. Actas Dermosifiliogr. 2009 Nov; 100(9): 756-8.

In this article by Juan de Azua, published in the second issue of Actas Dermosifiliográficas in 1909, the author reports his experience in 139 patients, most of them from Hospital San Juan de Dios, Madrid, Spain, and states he is sure that leprosy is a contagious disease. He discusses the factors related to contagion, which occurs in a closed and family environment, emphasizing socioeconomic factors such as hygiene and promiscuity. He considers direct contact to be important, though also recognizing indirect contact through drinks and food; he totally rejects a hereditary mechanism. Epidemiologically, he draws attention to the higher prevalence of the disease in Andalusia, though not forgetting "La Lepra de Ultramar [leprosy from distant lands]"-32 cases in Spaniards in Cuba and the Philippines. He believes isolation in hospitals or special sanatoriums, such as San Juan de Dios or San Lázaro in Santiago, Granada, and Seville, to be the best prophylaxis, and he considers it would be appropriate to create "Hospitals for poor lepers".

ÚLCERAS HANSÊNICAS

Ribeiro SLE, Pereira HLA, Souza LS. Manifestações sistêmicas e ulcerações cutâneas da hanseníase: diagnóstico diferencial com outras doenças reumáticas. Rev. bras. Reumatol. set.-out. 2009; 49(5): 623-9.

A hanseníase apresenta acometimento cutâneo e neurológico característicos; entretanto, as manifestações reumáticas são relativamente comuns sendo, em alguns pacientes, a queixa inicial. O presente relato de caso descreve uma paciente do sexo feminino, com hanseníase borderline, cuja manifestação inicial foi poliartrite simétrica, lesões cutâneas ulceradas em membros inferiores e manifestações sistêmicas simulando doença reumática. Os autores enfatizam a importância do diagnóstico diferencial do comprometimento sistêmico, articular e cutâneo na hanseníase com as doenças reumáticas.

Silva MT, Portaels F, Pedrosa J. Pathogenetic mechanisms of the intracellular parasite Mycobacterium ulcerans leading to Buruli ulcer. Lancet Infect Dis. 2009 Nov; 9(11): 699-710.

The necrotising skin infection Buruli ulcer is at present the third most common human mycobacteriosis worldwide, after tuberculosis and leprosy. Buruli ulcer is an emergent disease that is predominantly found in humid tropical regions. There is no vaccine against Buruli ulcer and its treatment is difficult. In addition to the huge social effect, Buruli ulcer is of great scientific interest because of the unique characteristics of its causative organism, Mycobacterium ulcerans. This pathogen is genetically very close to the typical intracellular parasites Mycobacterium marinum and Mycobacterium tuberculosis. We review data supporting the interpretation that M ulcerans has the essential hallmarks of an intracellular parasite, producing infections associated with immunologically relevant inflammatory responses, cell-mediated immunity, and delayed-type hypersensitivity. This interpretation judges that whereas M ulcerans behaves like the other pathogenic mycobacteria, it represents an extreme in the biodiversity of this family of pathogens because of its higher cytotoxicity due to the secretion of the exotoxin mycolactone. The acceptance of the interpretation that Buruli ulcer is caused by an intracellular parasite has relevant prophylactic and therapeutic implications, rather than representing the mere attribution of a label with academic interest, because it prompts the development of vaccines that boost cell-mediated immunity and the use of chemotherapeutic protocols that include intracellularly active antibiotics.