

BIOLOGIA MOLECULAR / GENÉTICA

Ranque B, Alter A, Schurr E, Abel L, Alcáis A. Leprosy: a paradigm for the study of human genetic susceptibility to infectious diseases. *Med Sci (Paris)* 2008; 24(5):491-7.

Fifty years ago, the first identification of a non Mendelian genetic contribution to the development of a common infectious disease, i.e. the association between malaria and sickle-cell trait, was shown using a supervised approach which tests a limited number of candidate genes selected by hypothesis. Since then, the few genes that were convincingly associated with susceptibility to human infectious diseases were identified following the same strategy. The study of leprosy has contributed to modifying this way of thinking. In the absence of a satisfying experimental model and because of the impossibility to grow the causative agent in vitro, the candidate gene approach has turned out to be of limited interest. Conversely, positional cloning led to the identification of two major genes involved in the control of the disease, establishing for the first time the oligogenic nature of a human genetic contribution to an infectious disease. It is likely that these major results obtained in leprosy and the recent burst of genomic tools will make the genome-wide screening (functional or positional) the main strategy of dissection of the genetic susceptibility to many common infectious diseases.

Alvarado-Navarro A, Montoya-Buelna M, Muñoz-Valle JF, López-Roa RI, Guillén-Vargas C, Fafutis-Morris M. The 3'UTR 1188 A/C polymorphism in the interleukin-12p40 gene (IL-12B) is associated with lepromatous leprosy in the west of Mexico. *Immunol Lett* 2008;118(2):148-51.

Leprosy is a chronic infectious disease caused by *Mycobacterium leprae*. IL-12 participates in the immune response against *M. leprae* by regulating T cell differentiation into the Th1-type response. Several single nucleotide polymorphisms have been identified in the IL-12 gene such as 3'UTR 1188 A/C polymorphism, which is associated with different diseases. However, the relationship of this polymorphism with the immune response in leprosy

has not been explored. In this case-control study, we evaluated 44 patients with lepromatous leprosy (LL) and 51 healthy subjects (HS). We aimed to determine the relationship between 3'UTR 1188 A/C polymorphism of IL-12 p40, mRNA expression, and soluble IL-12 concentration in LL patients and HS. Genotype frequencies were 41% A/A, 36% A/C, and 23% C/C in LL patients, and 47% A/A, 49% A/C, and 4% C/C in HS ($p < 0.05$). LL patients had a lower mRNA expression of IL-12 p40 gene, whereas HS had a higher expression level. Soluble IL-12 p40 concentration was higher in LL patients than in HS ($p < 0.05$). IL-12 p70 concentration did not differ between groups, and IL-12 p40 concentration was not significantly correlated with mRNA expression in either group. These data suggest that IL-12 p40 3'UTR 1188 A/C polymorphism is associated with greater susceptibility to lepromatous leprosy in patients from western Mexico, independently of IL-12 p40 and p70 expression levels.

Monot M, Honore N, Baliere C, Ji B, Sow S, Brennan PJ, et al. Are variable-number tandem repeats appropriate for genotyping *Mycobacterium leprae*? *Clin Microbiol* 2008; 46(7):2291-7.

Comparative genomics analysis of the Tamil Nadu strain of *Mycobacterium leprae* has uncovered several polymorphic sites with potential as epidemiological tools. In this study we compared the stability of two different markers of genomic biodiversity of *M. leprae* in several biopsy samples isolated from the same leprosy patient. The first type comprises five different variable-number tandem repeats (VNTR), while the second is composed of three single nucleotide polymorphisms (SNP). Contrasting results were obtained, since no variation was seen in the SNP profiles of *M. leprae* from 42 patients from 7 different locations in Mali whereas the VNTR profiles varied considerably. Furthermore, since variation in the VNTR pattern was seen not only between different isolates of *M. leprae* but also between biopsy samples from the same patient, these VNTR may be too dynamic for use as epidemiological markers for leprosy.

Literatura corrente em hanseníase

Marques MA, Neves-Ferreira AG, Silveira EK, Valente RH, Chapeaurouge A, Perales J, et al. Deciphering the proteomic profile of *Mycobacterium leprae* cell envelope. *Proteomics* 2008 ; 8(12):2477-91.

The complete sequence of the *Mycobacterium leprae* genome, an obligate intracellular pathogen, shows a dramatic reduction of functional genes, with a coding capacity of less than 50%. Despite this massive gene decay, the leprosy bacillus has managed to preserve a minimal gene set, most of it shared with *Mycobacterium tuberculosis*, allowing its survival in the host with ensuing pathological manifestations. Thus, the identification of proteins that are actually expressed in vivo by *M. leprae* is of high significance in understanding obligate, intracellular mycobacterial pathogenesis. In this study, a high-throughput proteomic approach was undertaken resulting in the identification of 218 new *M. leprae* proteins. Of these, 60 were in the soluble/cytosol fraction, 98 in the membrane and 104 in the cell wall. Although several proteins were identified in more than one sub-cellular fraction, the majority were unique to one. As expected, a high percentage of these included enzymes responsible for lipid biosynthesis and degradation, biosynthesis of the major components of the mycobacterial cell envelope, proteins involved in transportation across lipid barriers, and lipoproteins and transmembrane proteins with unknown functions. The data presented in this study contribute to our understanding of the in vivo composition and physiology of the mycobacterial cell envelope, a compartment known to play a major role in bacterial pathogenesis.

Lavania M, Katoch K, Katoch VM, Gupta AK, Chauhan DS, Sharma R, et al. Detection of viable *Mycobacterium leprae* in soil samples: Insights into possible sources of transmission of leprosy. *Infect Genet Evol* 2008; 8(5):627-31.

Leprosy has ceased to be a public health problem world wide, after the successful implementation of effective chemotherapy (MDT) and use of control measures. However, new cases of leprosy continue to occur. *Mycobacterium leprae* cannot be grown in any acceptable culture medium and besides the wild armadillos, there is no known animal reservoir for leprosy. The transmission of leprosy is believed to be due to a large extent by droplet discharge of bacilli through nose and mouth and to a lesser extent by direct contact of susceptible host with a patient for long duration. The exact role of the environment in the transmission dynamics is still speculative. In the present study, we have tried to detect viable *M. leprae* from soil samples in endemic areas by using molecular methods. Eighty soil samples were collected from villages of this area, DNA and RNA of *M. leprae* extracted and identified using specific *M. leprae* primers. PCR amplification was done and real-time RT-PCR was used to detect viable *M. leprae*. DNA targeting the 16S region of *M. leprae* was detected in 37.5%, whereas *M. leprae* RNA targeting the same region was detected in 35% of these samples. Of the total 80 samples, 40 were collected from residential areas of leprosy patients whereas 40 samples were from no-patient areas. Fifty-five percent positivity for 16S rRNA of *M. leprae* was observed from the "patient" area in comparison to 15% positivity from the "no-patient" area ($p < 0.001$). This study thus provides valuable information of presence of viable *M. leprae* in soil specimens, which would be of use in investigating the transmission dynamics in leprosy.

Sharma P, Chauhan DS, Upadhyay P, Faujdar J, Lavania M, Sachan S, et al. Molecular typing of Mycobacterium tuberculosis isolates from a rural area of Kanpur by spoligotyping and mycobacterial interspersed repetitive units (MIRUs) typing. *Infect Genet Evol* 2008; 8(5):621-6.

Molecular typing of Mycobacterium tuberculosis isolates has greatly facilitated the understanding of epidemiology of tuberculosis (TB). This study was done to characterize prevalent genotypes of M. tuberculosis on a collection of 97 isolates based on spoligotyping and mycobacterial interspersed repetitive units-variable number of tandem repeats (MIRU-VNTR) typing in rural area of Kanpur, North India. In this area different types of interventions are being undertaken and follow-up studies are progressing. Predominant spoligotypes prevalent in this region belonged to Central Asian-Delhi family (CAS1_Del) (37%), East African-Indian family (11%), T1 family (8%) and Beijing (4%) family. Highly distinct MIRU-VNTR genotypes were obtained. Significant spoligotypes such as Beijing and CAS1_Del type were further divided into subtypes with MIRU-VNTR. This preliminary study reveals that CAS is the most predominant family in this rural area of Kanpur. If confirmed in other areas, this combined approach of molecular typing can be preferably be used as first line tool for studying linkage and transmission dynamics of TB in India.

CLINICA/HANSENÍASE/COMPLICAÇÕES/REAÇÃO

Sarno EN, Illarramendi X, Nery JA, Sales AM, Gutierrez-Galhardo MC, Penna ML, et al. HIV-M leprae interaction: can HAART modify the course of leprosy? *Public Health Rep* 2008; 123(2):206-12.

It has been speculated that, as seen in tuberculosis, human immunodeficiency virus (HIV) and Mycobacterium leprae (M. leprae) co-infection may exacerbate the pathogenesis of leprosy lesions and/or lead to increased susceptibility to leprosy. However, to date, HIV infection has not appeared to increase susceptibility to leprosy. In contrast, initiation of antiretroviral treatment (ART) has been reported to be associated with anecdotal activation of M. leprae infection and exacerbation of existing leprosy lesions. To determine whether ART is associated with worsening of the manifestations of leprosy, a cohort of leprosy patients recruited between 1996 and 2006 at the Oswaldo Cruz Foundation (FIOCRUZ) Leprosy Outpatient Clinic in Rio de Janeiro, Brazil, was studied longitudinally. ART treatment of HIV/leprosy co-infection was associated with the tuberculoid type, paucibacillary disease, and lower bacillary loads. CD4 lymphocyte counts were higher among HIV/leprosy patients at the time of leprosy diagnosis, while viral loads were lower compared with the time of HIV diagnosis. The conclusion was that ART and immune reconstitution were critical factors driving the development and/or clinical appearance of leprosy lesions.

Literatura corrente em hanseníase

Abide JM, Webb RM, Jones HL, Young L. Three indigenous cases of leprosy in the Mississippi delta. South Med J 2008;101(6):635-8.

Three native-born patients from the Mississippi Delta presented with leprosy over a 13-month period. None had a history of foreign travel, contact with each other, or known leprosy patients. Two patients' lesions lacked anesthesia, and all had a history of armadillo exposure. These cases add to the association of armadillo exposure and the subsequent development of leprosy.

Aubry P, Bobin P. Leprosy and immune reconstitution syndrome in AIDS. Bull Soc Pathol Exot 2008; 101(1):58-9.

The immune reconstitution syndrome (IRS) has been typical of changes in the clinical presentations of opportunistic infections in AIDS patients since the introduction of HAART. Leprosy has joined the growing list of opportunistic infections associated with IRS.

Narang T, Dogra S, Kaur I. Localized lepromatous leprosy in household contact of multibacillary disease. J Cutan Med Surg 2008 May-Jun;12(3):139-41.

Lepromatous leprosy (LL) is a generalized disease, usually with numerous papules, nodules, or plaques containing abundant *Mycobacterium leprae* and affecting wide areas of the skin. AIM: To report on an LL patient presenting with two lesions on the face and to discuss its epidemiologic significance in the current context of leprosy elimination. METHODS: A 52-year-old housewife presented to our department with erythematous lesions over her face for 2 months. Her husband and son were treated for multibacillary leprosy 15 years previously. An infiltrated erythematous nodule was located over the right supraorbital area, and a single papule was present on the right eyelid. The rest of the examination was normal. RESULTS: A slit skin smear from the lesion revealed a bacillary index of 6+ and a morphologic index of 6%. A skin biopsy showed atrophic epidermis with an underly-

ing clear grenz zone; the dermis showed massive infiltration of foamy macrophages, filled with bacilli and a few lymphocytes. CONCLUSIONS: The presentation of LL or borderline lepromatous leprosy (BL) as a single cutaneous lesion (or localized lesions) is a rare presentation of multibacillary disease, and such cases can be undertreated. This case also highlights the need to further explore the role of immunoprophylaxis or chemoprophylaxis in the contacts of multibacillary cases.

Prabhu S, Rao R, Sripathi H, Rao L, Singh R. Localized and persistent erythema nodosum leprosum - a rare variant? Dermatol Online J 2008; 14(3):16.

Erythema nodosum leprosum (ENL) or Type-2 Lepra reaction is a manifestation of type III hypersensitivity response and usually occurs in certain cases of lepromatous and borderline lepromatous leprosy. It is usually generalized and evanescent, and responds well to oral corticosteroid therapy. Here we report an unusual case of persistent and localized ENL in a 19-year-old girl, which could be diagnosed with the aid of skin biopsy and histopathological examination.

Kharkar V, Bhor UH, Mahajan S, Khopkar U. Type I lepra reaction presenting as immune reconstitution inflammatory syndrome. Indian J Dermatol Venereol Leprol 2007; 7(4):253-6.

Immune reconstitution inflammatory syndrome (IRIS) is an unusual inflammatory reaction due to infectious and non-infectious causes occurring in human immunodeficiency virus (HIV)-infected patients. IRIS occurs after the initiation of antiretroviral therapy. There are no reports of type I lepra reaction due to IRIS in published literature from India. We report two cases of HIV-infected males who presented with borderline tuberculoid leprosy in type 1 reaction after the initiation of highly active antiretroviral treatment (HAART). Case 1 presented with multiple, tender, erythematous and hypoesthetic plaques on the trunk and extremities after 3 months of antiretroviral therapy. In case 2, type I lepra reaction was observed 2 months after the initiation of haart.

Kumari R, Thappa DM, Basu D. A fatal case of Lucio phenomenon from India. *Dermatol Online J* 2008; 14(2):10.

A 65-year-old man presented with cutaneous ulcerations involving the legs, hands, abdomen, buttocks, and pinna, along with fever, arthralgia, and anorexia for the prior 10 days. On cutaneous examination, dark, irregular-shaped bizarre erythematous purpuric spots and angulated ulcers were seen over bilateral, upper extremities and trunk including dorsum of hands, finger tips and the pinnae of both ears. Most striking were the presence of multiple deep ulcers covered with a blackish eschar and in some areas yellow slough eroding the subcutaneous tissue with ragged margins. These ulcers were distributed symmetrically over the thighs, lower legs and gluteal region. Slit-skin smear examination revealed a bacterial index (BI) of 6+ with globi from earlobes, ulcers 3+, eyebrows 3+ and normal skin 2+ and morphologically showed mainly solid (20-30%), fragmented (60-70%) and granular (5-10%) acid-fast bacilli. Biopsy from the ulcer margin revealed an ulcerated epidermis and dermis. The dermis had infiltrate of foamy macrophages, and evidence of ischemic necrotizing vasculitis, with fibrinoid necrosis and new vessel formation. There was presence of clumps of acid-fast bacilli (AFB) within macrophages, periadnexally, perivascularly, and also within endothelial cells. These clinical and histopathological features helped us to arrive at the diagnosis of Lucio phenomenon in an untreated case of Lucio leprosy which is rarely reported from areas other than Mexico.

DIAGNÓSTICO / DIAGNÓSTICO DIFERENCIAL

Concha R, Marcela CT, Laura M, Salazar S, Iván FS, Félix PC, et al.

Enfermedad de Hansen: revisión a propósito de un caso. *Rev chil infectol* 2008; 25(1):64-9.

Leprosy is a granulomatous disease affecting the skin and peripheral nerves caused by *Mycobacterium leprae*. The range of clinical forms varying from tuberculoid to lepromatous leprosy results from variations in the cellular immune response to the mycobacterium. Despite available combined drug-therapy, it continues to be a significant public health problem, carrying a strong stigma. Although recently there has been no native cases in Chile, a few imported cases have been diagnosed. We present a 56-year-old man who had lived in Paraguay for 8 years, and presented with leprosy 6 years after returning to Chile. The biology of leprosy, clinical features of the disease, current diagnostic criteria and approaches to treatment are discussed

Marques AS, Lastória JC, Putinatti MSMA, Camargo RMP, Marques MEA. Paracoccidioidomycosis: infiltrated, sarcoid-like cutaneous lesions misinterpreted as tuberculoid leprosy. *Rev Inst Med Trop* 2008; 50(1):47-50.

The authors report a case of paracoccidioidomycosis misinterpreted as tuberculoid leprosy, both on clinical and histological examination. Sarcoid-like cutaneous lesion as the initial presentation is rare in young patient with paracoccidioidomycosis and can simulate other infectious or inflammatory diseases. On histology, tuberculoid granuloma presented similar difficulties. Treatment with dapsone, a sulfonamide derivative, could have delayed the presumed natural clinical course to the classical juvenile type of paracoccidioidomycosis, observed only 24 months after the patient had been treated for leprosy.

Literatura corrente em hanseníase

Linder K, Zia M, Kern WV, Pfau RK, Wagner D. Relapses versus reactions in multibacillary leprosy: proposal of new relapse criteria. *Trop Med Int Health* 2008;13(3):295-309.

OBJECTIVES: To compare a new scoring system for multibacillary (MB) leprosy relapses, which combines time factor, risk factors and clinical presentation at relapse, to WHO criteria. **METHODS:** Data were collected on all relapses diagnosed between 1998 and 2004 at the Marie-Adelaide-Centre in Karachi, Pakistan, including case histories, clinical manifestations, follow-up, bacterial indices, treatment and contacts. For the diagnosis of MB relapses a simple scoring system was developed and validated on a data-set of mouse foot pads (MFP)-confirmed relapses (Leprosy Reviews, 76, 2005, 241). Its sensitivity was further evaluated in the Karachi relapse cohort. The P-value was calculated with McNemar's test with continuity correction. **RESULTS:** The new scoring system that combines time factor, risk factors and clinical presentation at relapse had a higher sensitivity in MFP-confirmed relapses than the WHO-criteria (95%vs. 65%, $P < 0.01$). The sensitivity of the scoring system was also significantly higher than the WHO criteria in the 57 cases of MB-relapses diagnosed in Karachi (72%vs. 54%, $P < 0.05$). **CONCLUSIONS:** This new simple scoring system for diagnosing MB-relapses in leprosy should be further validated in a prospective study to confirm its superior sensitivity and to evaluate the specificity of these criteria by using MFP-confirmation for patients presenting with signs of activity after treatment.

Goulart IM, Goulart LR. Leprosy: diagnostic and control challenges for a worldwide disease. *Arch Dermatol Res* 2008; 300(6):269-90.

Leprosy is a curable disease with well-defined etiology, but lacks better diagnostic tools, preventive and therapeutic strategies. The continued application of the Ridley-Jopling clinical classification that recognizes the natural diversity of the immune response has provided the basis for understanding leprosy, and this review proposes its implementation in all Reference Centers in order to standardize the diagnostic resources, aiming at the improvement of the disease control. Due to the broad bioepidemiological aspects of infection its eradication is difficult, and proper diagnosis of the disease and the correct clinical classification are required to ensure proper treatment. Tools and markers for diagnosis and prognosis, and the novel use of nanotechnology, as well as strategies for disease control and monitoring populations at higher risk are still continuous challenges, which will be specifically reviewed with additional insights. The use of the current diagnostic tools, such as ELISA and PCR has a very limited approach for leprosy that has been considered as a marginal disease; therefore, the current diagnostic tools must be applied extensively in the routine to accumulate clinical experience in order to improve their precise application, like what has been done in many other infectious diseases. Since a vaccine for leprosy presents an unpredictable future, the proposed chemoprophylaxis of contacts (healthy carriers and/or with subclinical infection) must also be employed in referral centers of endemic countries not only to evaluate its efficacy, but also because of the favorable cost-benefit ratio, given that there is no other available approach, besides the multi-drug therapy of patients. This strategy should readily be applied as a public health policy, and may lead to a substantial breakage of the transmission chain aiming a world without leprosy.

Trindade MA, Wen CL, Neto CF, Escuder MM, Andrade VL, Yamashitafuji TM, et al. Accuracy of store-and-forward diagnosis in leprosy. *J Telemed Telecare* 2008; 14(4):208-10.

Telemedicine might increase the speed of diagnosis for leprosy and reduce the development of disabilities. We compared the accuracy of diagnosis made by telemedicine with that made by in-person examination. The cases were patients with suspected leprosy at eight public health clinics in outlying areas of the city of São Paulo. The case history and clinical examination data, and at least two clinical images for each patient, were stored in a web-based system developed for teledermatology. After the examination in the public clinic, patients then attended a teaching hospital for an in-person examination. The benchmark was the clinical examination of two dermatologists at the university hospital. From August 2005 to April 2006, 142 suspected cases of leprosy were forwarded to the website by the doctors at the clinics. Of these, 36 cases were excluded. There was overall agreement in the diagnosis of leprosy in 74% of the 106 remaining cases. The sensitivity was 78% and the specificity was 31%. Although the specificity was low, the study suggests that telemedicine may be a useful low-cost method for obtaining second opinions in programmes to control leprosy.

Lyon S, Lyon AC, Da Silva RC, Grossi MA, Lyon SH, Bühner-Sékula S, et al. A comparison of ML Flow serology and slit skin smears to assess the bacterial load in newly diagnosed leprosy patients in Brazil. *Lepr Rev* 2008; 79(2):162-70.

INTRODUCTION: The ML Flow test is an immunochromatographic assay that detects IgM antibodies against *M. leprae*-specific anti-phenolic glycolipid I (PGL-I). In addition to slit skin smears stained by the Ziehl-Neelsen technique, it can be helpful in the operational classification of leprosy patients for treatment purposes. OBJECTIVE: This work studied the relationship between antibody levels as detected by semi-quantitative ML Flow serologic test and bacterial load as quantified by slit skin smear. PATIENTS AND METHODS: 135 patients with newly detected leprosy at the reference service in Sanitary Dermatology in Brazil had slit skin smears (registered as bacillary index - BI) and an ML Flow test (registered qualitatively and semi-quantitatively) performed at admission. A logistic regression and agreement measures (kappa index) were calculated. RESULTS: Slit skin smears were positive in 35.9% of patients and 57% of patients were seropositive for PGL-1 antibodies. Among the seropositive patients, 41.6% had five or fewer skin lesions, and 65.8% had more than one peripheral nerve involved. Slit skin smears were positive in only three seronegative patients (5.6%), and negative in 41.9% of seropositive patients. Patients with a BI of 4 + had an OR of 33 for being seropositive in comparison to those with a low BI. CONCLUSIONS: There is a correlation between serologic test and slit skin smear results. Therefore, an ML Flow test may become a useful tool in the clinical classification of leprosy, besides slit skin smears, which require a proper laboratory infrastructure and experienced personnel.

EDUCAÇÃO

Ukpe IS. Educational posters and leaflets on leprosy: raising awareness of leprosy for health-care workers in rural South Africa. *Public Health Rep* 2008; 123(2):217-21.

Leprosy is still occurring in the Republic of South Africa, but it has been eliminated as a public health problem. The country's leprosy care and control program is being provided as a primary health-care program within the general health-care services. Maintaining health workers' leprosy knowledge and awareness at the primary health-care level is one of the program's goals. In one of the country's rural areas, the availability of good-quality leprosy poster and leaflets at primary health-care facilities has been shown to contribute significantly to maintaining health workers' leprosy knowledge and awareness.

EPIDEMIOLOGIA

Domergue V, Clyti E, Sainte-Marie D, Huber F, Marty C, Couppié P. Leprosy in French Guyana: a retrospective study from 1997 to 2006. *Med Trop (Mars)* 2008;68(1):33-7.

French Guyana borders Brazil with the second highest number of cases of leprosy in the world. The purpose of this retrospective study of leprosy cases diagnosed in Guyana between January 1997 and December 2006 was to calculate the incidence of the disease and to identify any special clinical and epidemiological features. A total of 90 new cases were recorded during the study period for a mean incidence of 0.53 cases/10,000 inhabitants/year. Since this incidence is below the 1/10,000 threshold defined by the World Health Organization, leprosy is no longer considered as a major public health issue in French Guyana. However it must be noted that while the number of "native leprosy" cases has declined, the number of Brazilian cases has increased ($p < 0.01$). Brazilian leprosy has different epidemiological features, i.e., dominance of multibacillary forms and high incidence in gold panning and western regions of the country where the incidence is over 1/10,000 inhabitants/year.

EPIDEMIOLOGIA/CONTROLE/ELIMINAÇÃO

Silva SRA, Mathias TAF. Perspectivas de eliminação da hanseníase como problema de saúde pública no Estado do Paraná, Brasil. *Rep public health* 2008; 24(2):303-14.

A hanseníase, moléstia infecto-contagiosa endêmica, constitui ainda problema de saúde pública na maioria dos estados brasileiros, embora, nos últimos anos, venha apresentando queda importante em seu coeficiente de prevalência. Este estudo tem por objetivo analisar a perspectiva de eliminação da hanseníase no Estado do Paraná por meio dos coeficientes de detecção e de prevalência, nos anos de 2000 a 2005, além do sexo, idade, forma clínica, classificação operacional e número de lesões de pele. A fonte de informações foi o banco de dados do Sistema de Informação de Agravos de Notificação (SINAN) e o programa Tabnet. Os coeficientes de detecção e de prevalência da hanseníase no Paraná permaneceram sem alteração no período de estudo. Verificou-se, no Paraná, segundo as Regionais de Saúde, que o coeficiente de detecção da hanseníase foi, em sua maioria, alto ou muito alto. Quanto à prevalência, oito Regionais de Saúde alcançaram a meta de eliminação. Conclui-se que o Estado do Paraná está próximo de alcançar a meta de eliminação da hanseníase. Recomenda-se o fortalecimento das ações para que a eliminação da doença como um problema de saúde pública seja uma realidade.

Cardona-Castro N, Beltrán-Alzate JC, Manrique-Hernández R. Survey to identify mycobacterium leprae infected household contacts of patients from prevalent regions of leprosy in Colombia. Mem Inst Oswaldo Cruz 2008; 103(4):332-6.

Leprosy in Colombia is in the post-elimination phase; nevertheless, there are regions of this country where the incidence is still around 3-4/100,000. Early detection of leprosy patients is a priority for achieving control and elimination of leprosy; however, the clinical exam is not very sensitive and thus, the majority of patients are diagnosed only when they demonstrate lesions, and damage to the nerves and skin has already occurred. The goal of the present study was to identify *Mycobacterium leprae* infection and immune responses in household contacts (HHC) of leprosy patients from three prevalent regions of Colombia. Clinical examination, the Mitsuda test, evaluation of IgM anti-PGL-I in the serum, the bacillar index (BI), and polymerase chain reaction (PCR) from nasal swabs (NS) were performed for 402 HHC of 104 leprosy patients during a cross-sectional survey. Positive titers for IgM anti-PGL1 were found for 54 HHC, and PCR-positive NS for 22. The Mitsuda reaction was negative for 38 HHC, although three were positive for IgM anti-PGL-1 titers. The data document that leprosy transmission among HHC is still occurring in a non-endemic country

Kyaw K, Tsoh TM, Swe SY, Nagaoka Y, Takezaki S, Suzuki K, et al. Clinical analysis of multibacillary leprosy patients after 1-year fixed World Health Organization recommended multidrug therapy at Yangon General Hospital, Myanmar. J Dermatol 2008; 35(5):264-9.

This study included 200 randomly selected multibacillary leprosy cases who had completed 1 year of fixed World Health Organization recommended multidrug therapy (WHO-MDT) without prior dapsone (DDS) monotherapy. The time interval after release from treatment varied from a few months to 8 years. All cases were clinically reviewed in 2006 by comparison with their old clinical

records. Reactions, particularly reversal reactions, occurred frequently among patients who had completed MDT within the last 3 years. It was difficult to distinguish relapse cases and late reversal reactions in skin smear-negative multibacillary cases. Based on bacteriological and histological analyses, one patient was confirmed to have relapsed 1 year after release from treatment. The overall relapse rate was 0.5%. No drug resistance mutations were detected by polymerase chain reaction or dot blot hybridization. The present study indicates that it is important to follow up patients for several years after completion of MDT in order to detect possible lepra reactions and relapses.

Cardona-Castro N, Beltrán-Alzate JC, Manrique-Hernández R. Survey to identify Mycobacterium leprae-infected household contacts of patients from prevalent regions of leprosy in Colombia. Mem Inst Oswaldo Cruz 2008;103(4):332-6.

Leprosy in Colombia is in the post-elimination phase; nevertheless, there are regions of this country where the incidence is still around 3-4/100,000. Early detection of leprosy patients is a priority for achieving control and elimination of leprosy; however, the clinical exam is not very sensitive and thus, the majority of patients are diagnosed only when they demonstrate lesions, and damage to the nerves and skin has already occurred. The goal of the present study was to identify *Mycobacterium leprae* infection and immune responses in household contacts (HHC) of leprosy patients from three prevalent regions of Colombia. Clinical examination, the Mitsuda test, evaluation of IgM anti-PGL-I in the serum, the bacillar index (BI), and polymerase chain reaction (PCR) from nasal swabs (NS) were performed for 402 HHC of 104 leprosy patients during a cross-sectional survey. Positive titers for IgM anti-PGL1 were found for 54 HHC, and PCR-positive NS for 22. The Mitsuda reaction was negative for 38 HHC, although three were positive for IgM anti-PGL-1 titers. The data document that leprosy transmission among HHC is still occurring in a non-endemic country.

Literatura corrente em hanseníase

Galvão PR, Ferreira AT, Maciel MD, Almeida RP, Hinders D, Schreuder PA, et al. An evaluation of the Sinan health information system as used by the Hansen's disease control programme, Pernambuco State, Brazil. *Lepr Rev* 2008; 79(2):171-82.

BACKGROUND: Since the introduction of the national notifiable diseases information system (SINAN) in Pernambuco State, Brazil, in 1994, many problems have been encountered. The aim of this study was to evaluate the SINAN software, quality of data input, the transfer of the computerised data from the municipality to state levels, human resources and other factors associated with the health information system infrastructure (HIS). **METHODS:** A cross-sectional study was carried out in Pernambuco state, North-eastern Brazil, in 2005. A sample of health regions and municipalities was chosen. SINAN forms from those municipalities were analysed and the flow of notifications followed from municipal level to the regional and finally to the state. Professionals from health units, district, municipal and regional Hansen's Disease Control Programme (HDCP) and Epidemiological Surveillance System (ESS) coordinators, health secretaries and managers of the municipalities and health regions selected were interviewed. **RESULTS:** SINAN software is functioning up to expectation. However, at all levels of the health system, serious weaknesses not related to the SINAN software were found, varying from lack of human resources (limited number of staff and staff development), lack of infrastructure (office space, computers, supplies, etc.) to an absence of effective coordination, management and supervision of the HIS. **CONCLUSIONS:** Lack of reliable, complete and timely information, and especially the lack of widespread analysis and use of available information in planning and management of health services were the main weaknesses found. Many areas need urgent attention: the quality of patient examination, recording and reporting, the timely processing of quality data, the coordination and management of disease control programmes, and the use of HIS reports by the health services and health managers. Regular feedback, supportive supervision visits and annual reviews are essential to monitor the system and make sure that essential information is decentralised and used by

the primary health services and HDCP coordination. Assessing the quality of services from a client perspective would give additional information for the identification of strengths and weaknesses of the Hansen's disease (leprosy) services.

HANSENÍASE/ TRANSMISSÃO

Young SK, Ponnighaus JM, Jain S, Lucas S, Suneetha S, Lockwood DN, et al. Use of Short Tandem Repeat Sequences to Study *Mycobacterium leprae* in Leprosy Patients in Malawi and India. *PLoS Negl Trop Dis* 2008; 2(4):e214.

BACKGROUND: Inadequate understanding of the transmission of *Mycobacterium leprae* makes it difficult to predict the impact of leprosy control interventions. Genotypic tests that allow tracking of individual bacterial strains would strengthen epidemiological studies and contribute to our understanding of the disease. **METHODOLOGY/PRINCIPAL FINDINGS:** Genotyping assays based on variation in the copy number of short tandem repeat sequences were applied to biopsies collected in population-based epidemiological studies of leprosy in northern Malawi, and from members of multi-case households in Hyderabad, India. In the Malawi series, considerable genotypic variability was observed between patients, and also within patients, when isolates were collected at different times or from different tissues. Less within-patient variability was observed when isolates were collected from similar tissues at the same time. Less genotypic variability was noted amongst the closely related Indian patients than in the Malawi series. **CONCLUSIONS/SIGNIFICANCE:** Lineages of *M. leprae* undergo changes in their pattern of short tandem repeat sequences over time. Genetic divergence is particularly likely between bacilli inhabiting different (e.g., skin and nerve) tissues. Such variability makes short tandem repeat sequences unsuitable as a general tool for population-based strain typing of *M. leprae*, or for distinguishing relapse from reinfection. Careful use of these markers may provide insights into the development of disease within individuals and for tracking of short transmission chains.

HANSENÍASE/ EXPERIMENTAL/ TRANSMISSÃO

Clark BM, Murray CK, Horvath LL, Deye GA, Rasnake MS, Longfield RN. Case-control study of armadillo contact and Hansen's disease. *Am J Trop Med Hyg* 2008; 78(6):962-7.

Hansen's disease (HD) continues to have worldwide impact despite efforts to eradicate the disease. Although a definitive transmission mode has not been identified, data supports an association between HD and contact with the nine-banded armadillo. We conducted a case-control study of 28 HD patients to determine if there is an association between armadillo exposure and HD. There was no association between HD and place of birth or having hunted, consumed, or had direct or indirect contact with deer, birds, or squirrels. Univariate analysis showed that residence in Mexico ($P = 0.001$), hunting rabbits ($P = 0.04$), cleaning rabbits ($P < 0.001$), and armadillo exposure from hunting ($P = 0.005$), cleaning ($P = 0.004$), consuming ($P = 0.002$) them, or having direct armadillo contact ($P = 0.017$) were associated with HD. Multivariate analysis showed that eating armadillos ($P = 0.039$, odds ratio [OR] = 3.65, 95% confidence interval [CI] = 1.07-12.4), cleaning rabbits ($P = 0.018$, OR = 4.08, 95% CI = 1.27-13.1), and having lived in Mexico ($P = 0.006$, OR = 24.9, 95% CI = 2.52-245) were associated with HD.

Hamilton HK, Levis WR, Martiniuk F, Cabrera A, Wolf J. The role of the armadillo and sooty mangabey monkey in human leprosy. *Int J Dermatol* 2008; 47(6):545-50.

The armadillo was the first animal model of leprosy. Its role in the transmission of leprosy remains controversial. The sooty mangabey model of leprosy led to the discovery that rhesus monkeys were more susceptible to leprosy when coinfecting with simian immunodeficiency virus (SIV), but that leprosy may play a protective role against acquired immunodeficiency syndrome (AIDS) mortality. Recently, molecular methods have been developed for leprosy and may help resolve the role of zoonoses in

leprosy. **OBSERVATIONS:** The recent identification of a case of leprosy in a native-born American on the east coast of the USA and the identification of leprosy as an immunologic reconstitution inflammatory syndrome (IRIS) in human immunodeficiency virus (HIV)-positive cases raise the question of what role zoonoses may play in leprosy. **CONCLUSIONS:** Leprosy in armadillos and sooty mangabeys has been manipulated by human experimentation. In the case of the armadillo, further study, including molecular techniques, is required to elucidate the role of the armadillo as a zoonosis in human leprosy. Experimentation with the sooty mangabey led to the discovery of an interaction between SIV and leprosy in rhesus monkeys, and prompted the continued investigation of the relationship between HIV and leprosy.

HISTÓRIA

Santos FSD, Souza LPA, Siani AC. O óleo de chaulmoogra como conhecimento científico: a construção de uma terapêutica antileprótica. *Hist cienc saúde Manguinhos* 2008; 15(1):29-46.

Analisa os processos de assimilação e transformação de saberes e práticas terapêuticas que envolvem o uso de plantas medicinais, e destaca o uso, no combate à lepra, do óleo da chaulmoogra. Atenta para os diferentes modos de incorporação e transformação das chaulmoogras em conhecimentos validados cientificamente, tendo em vista a entrada em cena da 'chaulmoogra brasileira'. Privilegia a chegada dos derivados dessa planta à pauta de produção do Instituto Oswaldo Cruz (IOC), na década de 1920, estabelecendo nexos entre os diferentes processos produtivos e articulando-os ao contexto científico no período estudado. O óleo de chaulmoogra representou, até a década de 1940, a grande esperança para a tentativa de cura da lepra. Observa ainda que a terapêutica chaulmúgrica durante esse período, consolidou-se como um saber científico graças à realização de diversas pesquisas feitas em laboratórios de todo o mundo ocidental.

Literatura corrente em hanseníase

IMUNOLOGIA

Gomes GI, Nahn EP, Santos RK, Silva WD, Kipnis TL. The functional state of the complement system in leprosy. *Am J Trop Med Hyg* 2008;78(4):605-10.

Ninety-one patients with different clinical forms of leprosy, 36 lepromatous (LL), 33 tuberculoid (TL), and 22 dimorphic (DL), and 31 healthy volunteer donors were included in this study. Total complement system (CS) activity was assessed by hemolytic methods, whereas individual components were quantified by the enzyme-linked immunosorbent assay. Under conditions allowing initiation of cascade by the classic pathway (CP) but not alternative pathway (AP) activation, significant CS consumption was detected only in sera from patients with LL. In this group of patients, C4 but not factor B (fB) or C3 was significantly reduced, whereas mannose-binding lectin (MBL) serum levels were significantly higher. These results indicate that the CP is involved in CS activation in patients infected with *Mycobacterium leprae* manifesting LL clinical form of leprosy. An association is likely between circulating immune complexes and MBL high serum levels for initiation of CS activation in patients with LL form of leprosy

Sieling PA, Hill PJ, Dobos KM, Brookman K, Kuhlman AM, Fabri M, et al. Conserved mycobacterial lipoglycoproteins activate TLR2 but also require glycosylation for MHC class II-restricted T cell activation. *J Immunol* 2008; 180(9):5833-42.

CD4(+) T cell clones derived from a leprosy lesion and patient blood were used to monitor the isolation and identification of an Ag associated with the self-limited form of the disease. Biochemical purification and genetic analysis identified the T cell Ag as a conserved mycobacterial lipoglycoprotein LprG. LprG-mediated activation of CD4(+) T cells required specific MHC class II restriction molecules and intracellular processing. Although LprG activated TLR2, this alone was not sufficient to stimulate or inhibit T cell activation. A striking finding was that the carbohydrate moieties of LprG were required for optimal T cell activation, because recombinant LprG

produced in *Escherichia coli*, or recombinant LprG produced in *Mycobacterium smegmatis* and digested by alpha-mannosidase, did not activate T cells. This study demonstrates that the universe of bacterial T cell Ags includes lipoglycoproteins, which act as TLR2 ligands but also require glycosylation for MHC class II-restricted T cell activation in vivo.

Quesada-Pascual F, Jimenez-Flores R, Flores-Langarica A, Silva-Sanchez A, Calderon-Amador J, Mendez-Cruz R, et al. Characterization of langerhans cells in epidermal sheets along the body of Armadillo (*Dasypus novemcinctus*). *Vet Immunol Immunopathol* 2008 Aug 15;124(3-4):220-9.

Armadillos are apparently important reservoirs of *Mycobacterium leprae* and an animal model for human leprosy, whose immune system has been poorly studied. We aimed at characterizing the armadillo's langerhans cells (LC) using epidermal sheets instead of tissue sections, since the latter restrict analysis only to cut-traversed cells. Epidermal sheets by providing an en face view, are particularly convenient to evaluate dendritic morphology (cells are complete), spatial distribution (regular vs. clustered), and frequency (cell number/tissue area). Lack of anti-armadillo antibodies was overcome using LC-restricted ATPase staining, allowing assessment of cell frequency, cell size, and dendrites extension. Average LC frequency in four animals was 528 LC/mm², showing a rather uniform non-clustered distribution, which increased towards the animal's head, while cell size increased towards the tail; without overt differences between sexes. The screening of antibodies to human DC (MHC-II, CD 1a, langerin, CD86) in armadillo epidermal sheets, revealed positive cells with prominent dendritic morphology only with MHC-II and CD86. This allowed us to test DC mobilization from epidermis into dermis under topical oxazolone stimulation, a finding that was corroborated using whole skin conventional sections. We hope that the characterization of armadillo's LC will incite studies of leprosy and immunity in this animal model.

Misch EA, Macdonald M, Ranjit C, Sapkota BR, Wells RD, Siddiqui MR, et al. Human TLR1 deficiency is associated with impaired mycobacterial signaling and protection from leprosy reversal reaction. *PLoS Negl Trop Dis* 2008; 2(5):e231.

Toll-like receptors (TLRs) are important regulators of the innate immune response to pathogens, including *Mycobacterium leprae*, which is recognized by TLR1/2 heterodimers. We previously identified a transmembrane domain polymorphism, TLR1_T1805G, that encodes an isoleucine to serine substitution and is associated with impaired signaling. We hypothesized that this TLR1 SNP regulates the innate immune response and susceptibility to leprosy. In HEK293 cells transfected with the 1805T or 1805G variant and stimulated with extracts of *M. leprae*, NF-kappaB activity was impaired in cells with the 1805G polymorphism. We next stimulated PBMCs from individuals with different genotypes for this SNP and found that 1805GG individuals had significantly reduced cytokine responses to both whole irradiated *M. leprae* and cell wall extracts. To investigate whether TLR1 variation is associated with clinical presentations of leprosy or leprosy immune reactions, we examined 933 Nepalese leprosy patients, including 238 with reversal reaction (RR), an immune reaction characterized by a Th1 T cell cytokine response. We found that the 1805G allele was associated with protection from RR with an odds ratio (OR) of 0.51 (95% CI 0.29-0.87, $p = 0.01$). Individuals with 1805 genotypes GG or TG also had a reduced risk of RR in comparison to genotype TT with an OR of 0.55 (95% CI 0.31-0.97, $p = 0.04$). To our knowledge, this is the first association of TLR1 with a Th1-mediated immune response. Our findings suggest that TLR1 deficiency influences adaptive immunity during leprosy infection to affect clinical manifestations such as nerve damage and disability.

Peña MT, Adams JE, Adams LB, Gillis TP, Williams DL, Spencer JS, et al. Expression and characterization of recombinant interferon gamma (IFN-gamma) from the nine-banded armadillo (*Dasypus novemcinctus*) and its effect on *Mycobacterium leprae*-infected macrophages. *Cytokine* 2008;43(2):124-31.

Armadillos (*Dasypus novemcinctus*) manifest the full histopathological spectrum of leprosy, and are hosts of choice for in vivo propagation of *Mycobacterium leprae*. Though potentially useful as a model of leprosy pathogenesis, few armadillo-specific reagents exist. We have identified a region of high homology to the interferon gamma (IFN-gamma) of other mammals within the recently published armadillo whole genomic sequence. cDNA was made from ConA-stimulated armadillo peripheral blood mononuclear cells (PBMC), amplified, and cloned into a pET expression vector for transformation and over-expression in *Escherichia coli*. The recombinant protein (rDnIFN-gamma) was characterized by western blot and its biological function confirmed with bioassays including intracellular killing of *Toxoplasma gondii* and induction of indoleamine 2, 3-dioxygenase activity. In using rIFN-gamma to activate macrophages from mice, humans or armadillos, similar to humans, rIFN-gamma-activated armadillo MPhi did not produce nitrite and or inhibit the viability of *M. leprae* in vitro. Conversely, murine rIFN-gamma-activated mouse MPhi produced high levels of nitrite and killed intracellular *M. leprae* in vitro. These data indicate that the response of armadillo MPhi to rDnIFN-gamma is similar to that which occurs in humans, and demonstrates a potentially important value of the armadillo as a model in leprosy research.

Literatura corrente em hanseníase

Mastrangelo G, Marcer G, Cegolon L, Buja A, Fadda E, Scozzato L, et al. Med Hypotheses. 2008; 71(4):551-63. How to prevent immunological reactions in leprosy patients and interrupt transmission of Mycobacterium leprae to healthy subjects: two hypotheses.

The basis of World Health Organization strategy for leprosy elimination is that the only source and reservoir for infection are patients with the disease. It was assumed that multi drug therapy (MDT) would reduce transmission of Mycobacterium leprae, but there is no convincing evidence for this. Furthermore, even if MDT has been proved to be extremely effective against the infectious disease, a noticeable proportion of leprosy patients can suffer from immunologic hypersensitivity reactions which are now the most significant issue in the managements of the disease. In endemic areas it was found that: M. leprae survives outside human body; healthy individuals harbor M. leprae bacilli in nasal cavity and shed micro-organisms in environment; there is widespread subclinical transmission of M. leprae with transient infection of the nose resulting in the development of a mucosal immune response. This disparate clinical, epidemiologic, and microbiologic evidence leads to the first hypothesis: that antigenic load in local tissues, sufficient to trigger the immune response, comes from external supply of M. leprae organisms. The hypothyocyanite anion (OSCN(-)) is generated in vivo by the reaction of thiocyanate with hydrogen peroxide catalyzed by lactoperoxidase. OSCN(-) is an antimicrobial oxidizing agent that prevents growth of bacteria, fungi, and viruses. OSNC(-) exists in lower airway secretions and lung has never been reported to be affected by leprosy. There is a sufficient concentration of OSCN(-) in the saliva, and accordingly mouth is rarely affected by leprosy. By contrast, the concentration of this compound is low or nil in nasal and lacrimal secretions and leprosy very often affects

nose and eyes. The second hypothesis is that OSCN(-) may also protect from leprosy. Recently a method of OSCN(-) production, not involving enzymatic steps or use of toxic heavy-metal salts, has been patented. Studies on the susceptibility of M. leprae to hypothyocyanite could be carried out and, in case of positive results, the substance might be used in order to sterilize the nasal cavity of healthy carriers and prevent transmission of M. leprae to healthy subjects and to leprosy patients in whom it may trigger an immune response.

Dhungel S, Ranjit C, Sapkota BR, Macdonald M. Role of PGL-I of M. leprae in TNF-alpha production by in vitro whole blood assay. Nepal Med Coll J 2008 ;10(1):1-3.

Phenolic glycolipid-I (PGL-I) is known to be a major antigen of Mycobacterium leprae. We have studied the influence of PGL-I on the production of Tumour Necrosis Factor alpha (TNF-alpha) using the in vitro whole blood assay. Armadillo-derived M. leprae (ADML) are thought to be depleted of PGL-I during the purification process. M. leprae obtained from mouse foot pad material (MFPML) has been subjected to a less rigorous purification process; their PGL-I coating is therefore believed to be more intact than that of ADML. PGL-I or ADML alone induced the secretion of minimal levels of TNF-alpha in whole blood assay; when added in combination, higher levels of this cytokine were observed. The highest TNF-alpha response was seen following stimulation with MFPML. MFP material not infected with ML did not elicit any response. The difference in TNF-alpha response shown by ADML and MFPML was postulated to be largely due to the presence of higher levels of PGL-I in MFPML. This increase in TNF-alpha production suggests that PGL-I may play a significant role in the induction of TNF-alpha during natural infection.

Shannon E, Noveck R, Sandoval F, Kamath B. Thalidomide suppressed IL-1beta while enhancing TNF-alpha and IL-10, when cells in whole blood were stimulated with lipopolysaccharide. *Immunopharmacol Immunotoxicol* 2008;30(3):447-57.

Thalidomide is used to treat erythema nodosum leprosum (ENL). The events that precipitate this inflammatory reaction, which may occur in multibacillary leprosy patients, and the mechanism by which thalidomide arrests ENL, are not known. Thalidomide's ability to inhibit tumor necrosis factor alpha (TNF-alpha) in vitro has been proposed as a partial explanation of its effective treatment of ENL. In in vitro assays, thalidomide can enhance or suppress TNF-alpha. This is dependent on the stimulant used to evoke TNF-alpha; the procedure used to isolate the mononuclear cells from blood, and the predominant mononuclear cell type in the culture. To avoid artifacts that may occur during isolation of mononuclear cells from blood, we stimulated normal human blood with LPS and evaluated the effect of thalidomide and dexamethasone on TNF-alpha, and other inflammatory cytokines and biomarkers. Thalidomide suppressed interleukin 1 beta (IL-1beta) ($p = 0.007$), and it enhanced TNF-alpha ($p = 0.007$) and interleukin 10 (IL-10) ($p = 0.031$). Dexamethasone enhanced IL-10 ($p = 0.013$) and suppressed IL-1beta, TNF-alpha, interleukin 6 (IL-6), and interleukin 8 (IL-8) ($p = 0.013$). The two drugs did not suppress: C-reactive protein (CRP), Ig-superfamily cell-adhesion molecule 1 (ICAM 1), tumor necrosis factor receptor 1 (TNFR1), tumor necrosis factor receptor 2 (TNFR2), or amyloid A. In vitro and in vivo evidence is accumulating that TNF-alpha is not the primary cytokine targeted by thalidomide in ENL and other inflammatory conditions.

LABORATÓRIO CLÍNICO

Prasad CV, Kodliwadmth MV, Kodliwadmth GB. Erythrocyte glutathione peroxidase, glutathione reductase activities and blood glutathione content in leprosy. *J Infect* 2008; 56(6):469-73.

OBJECTIVES: Leprosy is a chronic granulomatous infection caused by *Mycobacterium leprae* involving cutaneous tissue and peripheral nerves producing skin lesions,

nerve degeneration, anaesthesia and deformities. In leprosy, the activated phagocytes produce reactive oxygen species (ROS) as a part of their microbicidal function. Such ROS are capable of damaging the host tissue by lipid peroxidation. Increased lipid peroxidation has been reported in leprosy. The glutathione antioxidant system with glutathione peroxidase (GSH-Px), glutathione reductase (GR) and glutathione (GSH) as components protect the cells from ROS toxicity and lipid peroxidation. The objective of the present study was to assess blood glutathione content and erythrocyte antioxidant enzyme activities of glutathione peroxidase and glutathione reductase in leprosy. DESIGN: The parameters were studied in 100 leprosy patients and 50 normal healthy controls. The data was analysed by grouping the patients into Ridley-Jopling (RJ) types [tuberculoid leprosy (TT), borderline tuberculoid leprosy (BT), borderline leprosy (BB), borderline lepromatous leprosy (BL), lepromatous leprosy (LL)] and into different levels of Bacteriological Index (BI) [bacteriologically negative (BI=0), BI=0.1-1, BI=1.1-2, BI=2.1-3, BI=3.1-4, BI=4.1-6]. METHODS: Venous blood sample was used for the study. The GSH level was estimated in the blood by DTNB [5,5'-dithiobis(2-nitrobenzoic acid)] reduction method. The enzyme activities were measured in the red blood cell haemolysate by kinetic methods using NADPH. RESULTS: GSH, GSH-Px and GR were significantly low in leprosy (total patients) as compared to the control group ($p < 0.001$). A progressive decrease in GSH level and enzyme activities was noted along the leprosy spectrum from TT to LL. A significant decline of GSH in BB ($p < 0.05$), BL ($p < 0.005$) and LL ($p < 0.001$); and of GSH-Px and GR in BT ($p < 0.05$, $p < 0.02$), BB ($p < 0.02$), BL ($p < 0.005$) and LL ($p < 0.001$) was noted as compared to controls. A significant lowering of GSH-Px in LL ($p < 0.005$); the GR in BB ($p < 0.02$), BL ($p < 0.05$) and LL ($p < 0.05$); and the GSH in BL ($p < 0.01$) and LL ($p < 0.001$) was noted in comparison to the TT group. The GSH and GSH-Px were significantly low in LL ($p < 0.05$) as compared to BT. A progressive decreasing trend in GSH level and enzyme activities was also noticed along the leprosy groups with advancing level of BI. The GSH, GSH-Px and GR were significantly low in BI levels 1.1-2 ($p < 0.005$, $p < 0.05$, $p < 0.02$), 2.1-3 ($p < 0.005$, $p < 0.001$, $p < 0.005$), 3.1-4 ($p < 0.005$) and 4.1-6 ($p < 0.01$, $p < 0.005$, $p < 0.05$) as compared to controls. A significant decline in

Literatura corrente em hanseníase

GSH was noted in BI levels 1.1-2 ($p < 0.005$), 2.1-3 ($p < 0.005$), 3.1-4 ($p < 0.005$) and 4.1-6 ($p < 0.01$) as compared to the bacteriologically negative group. The GSH-Px ($p < 0.05$) and GR ($p < 0.05$) were significantly low in BI levels 2.1-3, 3.1-4 and 4.1-6 as compared to the bacteriologically negative group. CONCLUSION: The findings suggest oxidative stress associated with diminished antioxidant defence potential in leprosy. The study identifies association of diminished antioxidant potential with bacterial load and type of leprosy.

MICROBIOLOGIA/MICOLOGIA/MICOBACTÉRIAS

Zuber B, Chami M, Houssin C, Dubochet J, Griffiths G, Daffé M. Direct visualization of the outer membrane of mycobacteria and corynebacteria in their native state. *J Bacteriol* 2008; 190(16):5672-80.

The cell envelope of mycobacteria, which include the causative agents of tuberculosis and leprosy, is crucial for their success as pathogens. Despite a continued strong emphasis on identifying the multiple chemical components of this envelope, it has proven difficult to combine its components into a comprehensive structural model, primarily because the available ultrastructural data rely on conventional electron microscopy embedding and sectioning, which are known to induce artifacts. The existence of an outer membrane bilayer has long been postulated but has never been directly observed by electron microscopy of ultrathin sections. Here we have used cryo-electron microscopy of vitreous sections (CEMOVIS) to perform a detailed ultrastructural analysis of three species belonging to the Corynebacterineae suborder, namely, *Mycobacterium bovis* BCG, *Mycobacterium smegmatis*, and *Corynebacterium glutamicum*, in their native state. We provide new information that accurately describes the different layers of the mycobacterial cell envelope and challenges current models of the organization of its components. We show a direct visualization of an outer membrane, analogous to that found in gram-negative bacteria, in the three bacterial species

examined. Furthermore, we demonstrate that mycolic acids, the hallmark of mycobacteria and related genera, are essential for the formation of this outer membrane. In addition, a granular layer and a low-density zone typifying the periplasmic space of gram-positive bacteria are apparent in CEMOVIS images of mycobacteria and corynebacteria. Based on our observations, a model of the organization of the lipids in the outer membrane is proposed. The architecture we describe should serve as a reference for future studies to relate the structure of the mycobacterial cell envelope to its function.

Miyagi H, Yamamoto Y, Kanamori S, Taira K, Asato Y, Myint CK, et al. Case of chromoblastomycosis appearing in an Okinawa patient with a medical history of Hansen's disease. *J Dermatol* 2008; 35(6):354-61.

Chromoblastomycosis is one of several chronic infectious skin diseases caused by various species of dematiaceous fungi. It is clinically characterized by verrucous skin eruptions and occurs most commonly in tropical and subtropical regions. In Okinawa, a subtropical area, there have been only three reported cases of chromoblastomycosis including the present one. Direct microscopic examination of crust specimens and findings of sclerotic cells in histopathology can confirm the diagnosis, and cultures of crust and/or tissue specimens can identify the causative fungi. We herein report the third case of chromoblastomycosis in Okinawa; it arose in an 87-year-old Japanese woman with a history of Hansen's disease, who lived in a leprosarium in Miyako Island. To identify the causative agent as *Fonsecaea pedrosoi*, we used the polymerase chain reaction and direct sequencing analysis in addition to the usual methods, which include 20% potassium hydroxide microscopy, histopathological confirmation of sclerotic cells by periodic acid-Schiff stain, culture by Sabouraud's glucose agar, slide culture method, and observation of conidia by scanning electron microscopic examination.

Morand JJ. Foot health in the tropics. *Med Trop (Mars)* 2008; 68(2):111-8.

The foot is particularly exposed to injury and infection in the tropical areas. This article provides a review of the main diseases affecting the foot in the tropics including leprosy, ainhum, ulceration due to *Mycobacterium ulcerans*, mycetoma, chromomycosis, Kaposi's sarcoma, elephantiasis, podoconiasis, dracunculosis, tungiasis, syphilis and endemic treponematosis, larva migrans, scytalidiosis, and envenomation. Prevention is essential

NEUROLOGIA/NEUROATOLOGIA

Kahawita IP, Walker SL, Lockwood DNJ. Leprosy type 1 reactions and erythema nodosum leprosum. *An bras dermatol* 2008; 83(1):75-82.

Leprosy reactions are a major cause of nerve damage and morbidity in a significant proportion of leprosy patients. Reactions are immunologically mediated and can occur even after successful completion of multi-drug therapy. This review focuses on the epidemiology, pathology and treatment of leprosy type 1 reactions, erythema nodosum leprosum and silent neuropathy.

Silva TP, Silva ACC, Baruque MGA, Oliveira RB, Machado MP, Sarno EN. Morphological and functional characterizations of Schwann cells stimulated with *Mycobacterium leprae*. *Mem Inst Oswaldo Cruz* 2008; 103(4):3639.

Nerve damage, a characteristic of leprosy, is the cause of patient deformities and a consequence of Schwann cells (SC) infection by *Mycobacterium leprae*. Although function/dysfunction of SC in human diseases like leprosy is difficult to study, many in vitro models, including SC lines derived from rat and/or human Schwannomas, have been employed. ST88-14 is one of the cell lineages used by many researchers as a model for *M. leprae*/SC interaction. However, it is necessary to establish the values and limitations of the generated data on the effects of *M. leprae* in these SC. After evaluating the cell line phenotype in the present study, it is close to non-

myelinating SC, making this lineage an ideal model for *M. leprae*/SC interaction. It was also observed that both *M. leprae* and PGL-1, a mycobacterial cell-wall component, induced low levels of apoptosis in ST88-14 by a mechanism independent of Bcl-2 family members

Prakash S, Dholakia SY. Hemicrania continua-like headache with leprosy: casual or causal association? *Headache* 2008; 48(7):1132-4.

Hemicrania continua is a strictly unilateral, moderate to severe, continuous, indomethacin-responsive primary headache disorder with ipsilateral autonomic cranial symptoms at the time of exacerbations. We describe a 30-year-old woman with a 4-month history of indomethacin-responsive hemicrania continua-like headache and one-month history of mononeuritis multiplex due to leprosy. Indomethacin was successfully weaned off after completion of antileprotic therapy.

Silva TP, Silva AC, Baruque Mda G, Oliveira RB, Machado MP, Sarno EN. Morphological and functional characterizations of Schwann cells stimulated with *Mycobacterium leprae*. *Mem Inst Oswaldo Cruz* 2008; 103(4):363-9.

Nerve damage, a characteristic of leprosy, is the cause of patient deformities and a consequence of Schwann cells (SC) infection by *Mycobacterium leprae*. Although function/dysfunction of SC in human diseases like leprosy is difficult to study, many in vitro models, including SC lines derived from rat and/or human Schwannomas, have been employed. ST88-14 is one of the cell lineages used by many researchers as a model for *M. leprae*/SC interaction. However, it is necessary to establish the values and limitations of the generated data on the effects of *M. leprae* in these SC. After evaluating the cell line phenotype in the present study, it is close to non-myelinating SC, making this lineage an ideal model for *M. leprae*/SC interaction. It was also observed that both *M. leprae* and PGL-1, a mycobacterial cell-wall component, induced low levels of apoptosis in ST88-14 by a mechanism independent of Bcl-2 family members.

Literatura corrente em hanseníase

Gabelle A, Vallat JM, Flageul B, Andre P, Camu W. Sensory-motor neuropathy: a slow and misleading case of leprosy. Rev Neurol (Paris) 2008.

The diagnostic process of sensory-motor neuropathies is difficult. Atypical variants and rare etiologies also contribute to delay the diagnosis. We report the case of a 70-year-old woman with slowly progressive asymmetric axonal sensory-motor neuropathy. Leprosy was identified after an eight-year delay. Nerve biopsy was required to establish the diagnosis: electron microscopy revealed debris of Hansen's bacillus in the nerve. Treatment was fully curative after several months. Leprosy is a rare cause of neuropathy in Europeans. Systematic inquiry about travel to endemic areas would be helpful in establishing the diagnosis. In such cases, nerve biopsy is crucial.

Slim FJ, Hoeksma AF, Maas M, Faber WR. A clinical and radiological follow-up study in leprosy patients with asymptomatic neuropathic feet. Lepr Rev 2008; 79(2):183-92

OBJECTIVES: An MRI study done in 2000 on 10 leprosy patients with neuropathic feet, without clinical complications such as ulcerations, osteomyelitis or Charcot deformities revealed abnormalities in nine patients, with degradation, interruption of subcutaneous fat and effusion/synovitis, all located in the first metatarsophalangeal (MTP) region. Since these MRI abnormalities may precede clinical complications of the foot, a follow-up study was performed. **DESIGN:** A new evaluation was based on a clinical examination and an MRI of the same patients who participated in the initial study. **RESULTS:** Four patients were lost to follow-up. Average follow-up period was 4-6 years. MRI abnormalities in the MTP 1 region in the first study were no longer visible in three patients, but were still present in two patients. In six patients new MRI findings were found, without clinical evidence of ulceration, osteomyelitis or Charcot deformity. No relationship was found between MRI findings in the MTP 1 region at the start of the study and the development of foot ulcers, callus or skin fissures in the MTP 1 region during follow-up. **CONCLUSION:** MRI findings of interruption and

infiltration of the subcutaneous fat in leprosy patients with uncomplicated neuropathic feet do not necessarily have any clinical implication for the development of future foot problems.

McCormick CA, Rath S, Patra PN, Pereira J, Wilkinson M. A qualitative study of common functional problems experienced by people with complete ulnar nerve paralysis. Lepr Rev 2008; 79(2):154-61.

OBJECTIVES: To identify the most common functional problems caused by ulnar nerve palsy. This study is the first phase in the process of developing a patient-centred hand function questionnaire specific for ulnar palsy. **DESIGN:** Twenty-five participants with complete irreversible ulnar nerve palsy were asked to record the five main problems they had because of their hand deformity in the week before they came to hospital. They ranked these problems in order of priority. The participants had all been referred to LEPRO-HOINA Leprosy Reconstructive Surgery Hospital, Muniguda, Orissa, India for tendon transfer surgery. **RESULTS:** Thirty-nine problems were experienced by the participants; 37 of these were functional problems. Five problems had a prevalence of $\geq 40\%$, these were holding soap (68%), eating (56%), buttoning (48%), holding a glass (44%) and lifting small objects (44%). Further analysis according to whether the left or right hand was affected was performed; 92% of participants with right ulnar nerve palsy had a problem eating compared to only 20% of those with left ulnar palsy. Eating was ranked as the most important problem by 28% of participants, holding a glass by 12% and holding soap by 8%. **CONCLUSIONS:** Ulnar nerve palsy had an important impact on basic activities of daily living—eating, washing, and drinking. Not only are these activities themselves affected but the person with a hand deformity avoids social situations where it will be noticed. This study indicates that there is a need to identify and treat people who have ulnar nerve palsy in order that they can be integrated into society, become independent with activities of daily living and earn an income.

Khambati FA, Shetty VP, Ghate SD, Capadia GD, Pai VV, Ganapati R. The effect of corticosteroid usage on the bacterial killing, clearance and nerve damage in leprosy: a prospective cohort study: part 1--study design and baseline findings of 400 untreated multibacillary patients. *Lepr Rev* 2008 ; 79(2):134-53.

OBJECTIVE: To investigate possible adverse effects of therapeutic usage of corticosteroids on the killing and clearance of *M. leprae* and the clearance of granuloma, in patients with multibacillary (MB) leprosy. **DESIGN:** A cohort of 400 untreated MB patients were sub-grouped into those to be treated with corticosteroids (prednisolone 40 mg daily tapered to 5 mg over 12 weeks) along with MB-MDT for reaction and/or neuritis or silent neuropathy (SN) of <6 months duration (group A), and those with no reaction and to be treated with MDT only (group B). Clinical, bacteriological, histopathological and neurological test findings at fixed time points were compared. Analysis was performed using SPSS version 10.0. The significance of association was tested using Chi-square test. In the current report, we describe the study design and baseline findings of 400 untreated MB patients, with special emphasis on differences between patients in groups A and B. **RESULTS:** At baseline, applying Ridley-Jopling classification, 39% patients were BT, 20% BB, 24% BL, 12% sub-polar LL and 5% pure neural (PN). Overall, 60% patients were slit skin smear (SSS) negative and 33% presented with disability either grades 1 or 2. Overall 140/400 (35%) patients presented with reaction and/or neuritis and 11/400 (3%) presented with SN of <6 months duration. Comparing groups A and B, the percentage of patients presenting with DG2 was significantly higher in group A (43%). By clinical tests, monofilaments (MF) and voluntary muscle testing (VMT), the percentage of patients and nerves showing functional impairment was also significantly higher in group A. However, in the more sensitive nerve conduction velocity (NCV) test, the percentage of patients that showed nerve abnormalities was closely comparable; 94% and 91% in groups A and B respectively while number of affected nerves was higher in group A. **CONCLUSION:** At baseline, as recorded by NCV, peripheral nerve function abnormality was observed in almost all the MB patients regardless of reaction; but among those presenting with reaction or neuritis, the nerve damage was more severe and extensive.

PREVALÊNCIA

Carsalade GY, Receveur MC, Ezzedine K, Saget J, Achirafi A, Bobin P, et al. Delayed home screening of leprosy; experience of the screening team in Mayotte. *Bull Soc Pathol Exot* 2008; 101(1):32-5.

Mayotte, a French territory island located in the Indian Ocean near Madagascar, remains a leprosy endemic area. In 2006, leprosy was still a problem of public health with a prevalence of 3.94 per 10,000 inhabitants. There is practically no formal consensus about active screening (AS) on an index case. According to teams and their related staffs, the AS concerns intradomiciliary contact individuals (IDC) restrictively or extended to extra-domiciliary social and professional contacts. Date, number and frequency of these investigations depend on each team. Between 1997 and 2003, there was no AS planned in Mayotte, but all index case individuals have been encouraged to propose a screening to their relatives through specific campaign information and education. This procedure allowed to identify 10 new cases of leprosy infection among the IDC. Concurrently 12 IDC cases have been diagnosed by health workers. In 2003, we performed a postponed AS within IDC of every Mahorais case registered by passive detection between 1997 and 2003. 325 IDC have been examined and 15 new cases have been detected. All these new cases showed early leprosy features: 14 were paucibacillary forms, among which 9 cases with an isolated cutaneous lesion (7 had an infracentimetric lesion). One patient had multibacillary disease although he presented with an isolated skin lesion which developed within the 6 previous months. None presented with disability. Our results suggest that passive detection even reinforced by repeated individual information and education about leprosy is neither appropriate nor effective. The postponed AS seems to favour an increased self-esteem and a better involvement of the index patient in sanitary education together with the screening of his relatives. In the Mayotte background, the postponed AS has not been associated with a significant delay for diagnosis. Although WHO recommendations are to abandon immediate AS of IDC and to promote self-screening for leprosy our study suggests an intermediate position, namely delayed active screening for an enhanced effective detection.

PREVALÊNCIA / INCAPACIDADE

Van Brakel WH, Officer A. Approaches and tools for measuring disability in low and middle-income countries. *Lepr Rev* 2008; 79(1):50-64.

To review the current state-of-the-art of measuring disability in the context of countries where leprosy is endemic. **BACKGROUND:** Estimates of the prevalence of disability are often based on scanty data, collected with a myriad of different instruments. This is true for all four components of the International Classification of Functioning, Disability and Health (ICF); 1) body functions and structures, 2) activities and participation, 3) personal factors and 4) environmental factors, and for disability-related quality of life. There is an urgent need for data on leprosy-related disability, as well as for data on disability due to other causes. Data is needed as baseline for rehabilitation programmes, individual interventions, for programme monitoring and evaluation and for advocacy. **RESULTS:** Measurement instruments and qualitative data collection techniques now exist which are directly applicable in the context of most leprosy-endemic countries. We discuss several instruments compatible with the ICF conceptual framework. A validated generic instrument for measuring impairment is currently not available. For measuring activity and participation, we recommend the WHODAS, the SALSA scale and the Participation Scale. We recommend an inclusive focus, where people with leprosy-related disability are seen as a sub-group of people with disability in the wider context, since many of their needs are the same as those of others. The need for validation and collection of normative reference data is also discussed. **CONCLUSIONS:** Programmes and research projects should choose an appropriate set of tools and methods and seek to apply these systematically. This choice should be guided by data on the validity of these tools in the concerned context. Instruments should be revalidated formally in every new context. Similarly, locally relevant normative data should be collected and applied to ensure that decisions are based on valid interpretations and conclusions.

REABILITAÇÃO

Velema JP, Ebenso B, Fuzikawa PL. Evidence for the effectiveness of rehabilitation-in-the-community programmes. *Lepr Rev* 2008; 79(1):65-82.

The present literature review identified 29 reports from 22 countries in Asia, Africa and Central America reporting on the outcomes of rehabilitation-in-the-community programmes in low and middle income countries published between 1987 and 2007. Interventions included home visits by trained community workers who taught disabled persons skills to carry out activities of daily living, encouraged disabled children to go to school, helped find employment or an income generating activity, often involving vocational training and/or micro-credit. Many programmes had a component of influencing community attitudes towards disabled persons. The information collected shows that such programmes were effective in that they increased independence, mobility and communication skills of disabled persons, helped parents of disabled children to cope better and increased the number of disabled children attending schools. Economic interventions effectively increased the income of disabled persons although they rarely made them financially independent. CBR activities result in social processes that change the way community members view persons with disabilities, increase their level of acceptance and social inclusion and mobilise resources to meet their needs. In most countries, coverage of CBR programmes is inadequate. CBR initiatives appear most beneficial to those who have mild physical disability and can communicate verbally. There is a need to invest in the generation of quality evidence about the outcome and impact of rehabilitation-in-the-community programmes to ensure its continued support.

Finkenflügel H, Rule S. Integrating community-based rehabilitation and leprosy rehabilitation services into an inclusive development approach. *Lepr Rev* 2008; 79(1):83-91.

Community-based rehabilitation (CBR) has been described as a strategy for leprosy rehabilitation. Developments in CBR and leprosy rehabilitation services, including Socio-economic rehabilitation (SER) show that both approaches aim to become part of a community development process. The basic assumption is that people with disabilities will benefit most from being included in mainstream programmes implemented in their own community, e.g. programmes aiming to improve livelihood. These developments have a decisive impact on the roles of all people involved in the rehabilitation process. Where the emphasis in the rehabilitation process shifts to the community and becomes part of community development, the rehabilitation workers need different competencies than were required in vertical disability programmes. This article focuses on the changing roles of mid-level rehabilitation workers and trainers and therapists. In many programmes a mid-level cadre was introduced to work with people with disabilities and their families. Consequently, trainers and therapists have moved away from direct, hands-on interventions and focussed on training this mid-level cadre and offering specialised referral services. This system was primarily developed to provide treatment at all levels, including community level. However, when rehabilitation becomes part of a community development process there is a need for 'change agents' and a structure that supports them. The success of integrating disability specific programmes like CBR and SER, into inclusive development programmes will depend largely on the extent to which rehabilitation workers are able to reinvent themselves as 'change agents' and redefine their roles, positions, and competencies.

Khasnabis C, Motsch KH. The participatory development of international guidelines for CBR. *Lepr Rev* 2008; 79(1):17-29.

PURPOSE: The CBR Guidelines are being developed by UN Agencies and civil society groups including disabled people's organisations (DPO). The aim of the CBR guidelines is to enhance the quality of life of people with disabilities including those affected by leprosy. Strong linkages between leprosy programmes and CBR will optimise the benefit of medical care and ensure leprosy-affected people access all relevant services that promote inclusion and participation. **BACKGROUND:** The World Health Organisation introduced the concept Community Based Rehabilitation (CBR) in the early 1980s. CBR was designed to enhance the quality of life for people with disabilities through community initiatives. To facilitate this, WHO published a CBR Manual 'Training in the community for people with disabilities' in 1989. Since then there have been many developments within and outside the disability sector. Based on these global developments and as a result of stakeholder consultation, ILO, UNESCO and WHO updated the CBR Joint Position Paper (2004) and restructured CBR as a strategy for rehabilitation, equalisation of opportunities, poverty reduction and social inclusion of people with disabilities. The purpose of this Joint Position Paper was to describe and support the concept of CBR as it is evolving, with an emphasis on human rights and a call for action against poverty. The Convention on the Rights of Persons with Disabilities aims to ensure that they enjoy human rights on an equal basis with others. Guidelines on how to implement CBR respond to the demands created by the publication of the Joint Position Paper and The Convention on the Rights of Persons with Disabilities. **RESULTS:** The CBR Guidelines are being developed by three UN agencies: WHO, ILO and UNESCO. It is being actively supported by 13 International Non Governmental Organisations (NGO) including Disabled People's Organisations (DPO). Over 150 experts from across the globe have contributed to the draft guidelines which are being field tested in 25 countries. The guidelines have five major components: health, education, livelihood, social and empowerment. Beside these five components, the Guidelines also focus on management of some special scenarios including CBR

Literatura corrente em hanseníase

and HIV/AIDS, CBR and leprosy, CBR and mental health and CBR in crisis situations. The CBR guidelines also underline that people with leprosy-related disability are seen as members of the disability community in the wider context given the shared experiences and challenges. CONCLUSIONS: The CBR guidelines are an important step forward in promoting CBR as a community based inclusive development strategy. The guidelines focus on meeting basic needs, reducing poverty, accessing benefits of mainstream developmental initiatives, inclusive community and empowering people with disabilities and their families. It also focuses on implementing the Convention on the Rights of Persons with Disabilities using community-based initiatives. People with leprosy are often neglected by traditional CBR programmes. These guidelines make the case for including people with leprosy in CBR programmes and in the community.

REUMATOLOGIA/ HANSENÍASE

Mandal SK, Sarkar RN, Sarkar P, Datta S, Bandyopadhyay R, Bandyopadhyay D, et al. Rheumatological manifestations of leprosy. *J Indian Med Assoc* 2008 Mar;106(3):165-6.

Rheumatological manifestations are common in leprosy. A study was conducted among 30 patients to observe the prevalence and spectrum of rheumatological manifestations in leprosy. Seventeen patients were referred from leprosy clinic from 287 consecutive leprosy cases and 13 patients presented de novo at the rheumatology clinic and later diagnosed to have leprosy. In the first group, the most common manifestation was small and large joints polyarthritis resembling rheumatoid arthritis found in 64.7% cases and in the second group tenosynovitis (38.5%) was the commonest. Rheumatoid factor was positive in 60% cases.

Mandal SK, Sarkar RN, Sarkar P, Datta S, Bandyopadhyay R, Bandyopadhyay D, et al. Rheumatological manifestations of leprosy. *J Indian Med Assoc* 2008 ;106(3):165-6.

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SOCIAL/ECONÔMICA

Klerk T. Funding for self-employment of people with disabilities. Grants, loans, revolving funds or linkage with microfinance programmes. *Lepr Rev* 2008; 79(1):92-109

In 2005, Handicap International commissioned a study on the practices of funding for self-employment activities of people with disabilities (PWD), with a special focus on access to microfinance. The overall goal of the study was to produce a framework document highlighting good practices, strategies, tools and operational methods that guarantee the efficiency and sustainability of self-employment projects for PWDs. The first phase of the study consisted of a literature review and a worldwide survey. Through this first phase the research team identified the most innovative programmes for further analysis through field visits. In the second phase field visits were conducted in Afghanistan, Bangladesh, Ethiopia, India,

Kenya, Nicaragua and Uganda, while regional workshops were organised in Dhaka and Nairobi. Phase three involved consolidation and analysis of the information and finally drafting of the framework document. This paper summarises the findings and good practices as presented in the framework document, based on the results of the literature review, the survey and the field research. It is not a scientific paper, i.e. it doesn't contain a discussion of the literature reviewed or systematic reference to sources, the same as the document on which it is based, as it is primarily meant for 'practitioners'. A main finding of the study was that there is no single 'best solution' to funding of self employment activities. While inclusion of PWDs in existing microfinance institutions (MFIs) is the preferred strategy, guaranteeing efficiency, sustainability and future access to funding for the target group, it was found that in reality many PWDs do not have access to microfinance programmes. This can be explained by stigmatisation of PWDs by staff of MFIs, who do not believe in their income earning and repayment capacity, and self-exclusion by PWDs. To fight against it projects have been set-up linking MFIs with programmes for PWDs, focusing on better information exchange between both parties respectively on disability for MFIs and the characteristics of microfinance for programmes for PWDs. Other programmes experiment with special credit lines or guarantee funds, placed at the disposal of MFIs and earmarked for loan disbursement for PWDs, to facilitate their inclusion. Another reason for non-inclusion is the vulnerability of many PWDs. Many of them have no prior business experience, while many MFIs only provide loans to clients with an existing business. Vocational and/or business training and raising of their self-confidence, to be assured by a programme for PWDs, is often required prior to setting-up of a self-employment activity and taking a loan. If not prepared to run a 'business' successfully, taking a loan will present a too great a risk for themselves, getting indebted, and for the MFI. 'Start-up' grants for

business-starters and revolving funds managed by PWD programmes, are other approaches practised by PWD programmes, of which the pros and cons are discussed in the study. A major weakness of many MFIs is that they do not reach the most vulnerable clients, including many of the PWDs, and their weak presence in rural areas especially in Africa. MFIs have to look for innovative approaches to deepen their outreach. The self-help group approach in India, starting with the clients' own savings from which loans can be disbursed to the group members while linking the well-performing groups to banks for access to bank loans, is such a new approach. It is practised by The Leprosy Mission Trust in India. In Africa, some international NGOs started with similar 'community based saving and lending groups'.

TERAPÊUTICA

Pardillo FE, Burgos J, Fajardo TT, Dela Cruz E, Abalos RM, Paredes RM, et al. **Powerful bactericidal activity of moxifloxacin in human leprosy. Antimicrob Agents Chemother 2008; 52(9): 3113-7.**

In a clinical trial of moxifloxacin in eight multibacillary leprosy patients, moxifloxacin proved highly effective. In all trial patients, a single 400-mg dose of moxifloxacin resulted in significant killing ($P \leq 0.006$) of *Mycobacterium leprae*, ranging from 82% to 99%, with a mean of 91%. In all instances, no viable bacilli were detected with an additional 3 weeks of daily therapy, this observed rapid bactericidal activity being matched previously only by rifampin. On moxifloxacin therapy, skin lesions cleared exceedingly rapidly with definite improvement observed consistently after eight doses and progressive resolution continuing for the 56 days of the trial. Side effects, toxicities, and laboratory abnormalities were mild, not requiring discontinuation of therapy.

TERAPÊUTICA / COMPLICAÇÕES / REAÇÕES ADVERSAS EXPERIMENTAL

Moraes NV, Mello MH, Souza AM, Sampaio SV, Queiroz RHC. Potencialização do efeito metemoglobinizante da dapsona em ratos pela N-acetilcisteína. *Rev bras cienc farm* 2008; 44(1): 97-104.

Dapsona (DDS) (4,4'diaminodifenilsulfona), fármaco de escolha para o tratamento da hanseníase, freqüentemente induz anemia hemolítica e metemoglobinemia. A N-hidroxilação, uma de suas principais vias de biotransformação, é constantemente relacionada com a metemoglobinemia observada com o uso do fármaco. Com o objetivo de prevenir a hemotoxicidade induzida pela DDS, N-acetilcisteína, fármaco precursor de glutathione, foi administrada em associação com DDS em ratos machos Wistar pesando 220-240 g. Os animais foram anestesiados e o sangue coletado da aorta para determinação da concentração plasmática de DDS por CLAE, determinação dos níveis de metemoglobina e de glutathione eritrocitária por espectrofotometria, e avaliação de parâmetros bioquímicos e hematológicos. Os resultados obtidos mostraram que a N-acetilcisteína potenciou o efeito metemoglobinizante da dapsona devido ao aumento de sua concentração plasmática e conseqüente aumento da formação da N-hidroxilamina. Concluímos que as interações medicamentosas com a dapsona exigem estudos individualizados a fim de evitar os efeitos adversos do fármaco.

Paina FA, Queiroz RHC, Souza AM. Alterações hematológicas, hemostáticas e bioquímicas induzidas pela clofazimina e claritromicina, em doses única e múltiplas, em ratos. *Rev Soc Bras Med Trop* 2008; 41(3):282-7.

Claritromicina e clofazimina têm sido utilizadas no tratamento da hanseníase, tuberculose e infecções causadas pelo complexo *Mycobacterium avium*. Como os dados sobre a toxicidade de esquemas terapêuticos que incluem estes fármacos são escassos, este estudo teve como objetivo determinar os efeitos adversos destas terapias, por meio da avaliação dos parâmetros hematológicos, hemostáticos e bioquímicos. Os fármacos foram administrados em ratos machos Wistar, em monoterapia, em regime de doses única e múltipla. Claritromicina provocou aumento de leucócitos mono e polimorfonucleares. Ambos os fármacos inverteram a proporção entre células mono e polimorfonucleares e provocaram aumento do número de células polimorfonucleares e células em degeneração. Clofazimina e claritromicina prolongaram o tempo de protrombina e claritromicina também prolongou o tempo de tromboplastina parcial ativa. Claritromicina causou aumento de bilirrubinas total e direta e, ambos os fármacos, elevaram os níveis plasmáticos de gama-glutamyltransferase. Portanto, clofazimina e claritromicina induzem alterações hematológicas, hemostáticas e hepáticas.

Veggi LM, Pretto L, Ochoa EJ, Catania VA, Luquita MG, Taborda DR, et al. Dapsone induces oxidative stress and impairs antioxidant defenses in rat liver. *Life Sci* 2008; 83(5-6):155-63.

Dapsone (DDS) is currently used in the treatment of leprosy, malaria and in infections with *Pneumocystis jirovecii* and *Toxoplasma gondii* in AIDS patients. Adverse effects of DDS involve methemoglobinemia and hemolysis and, to a lower extent, liver damage, though the mechanism is poorly characterized. We evaluated the effect of DDS administration to male and female rats (30 mg/kg body wt, twice a day, for 4 days) on liver oxidative stress through assessment of biliary output and liver content of reduced (GSH) and oxidized (GSSG) glutathione, lipid peroxidation, and expression/activities of the main antioxidant enzymes glutathione peroxidase, superoxide dismutase, catalase and glutathione S-transferase. The influence of DDS treatment on expression/activity of the main DDS phase-II-metabolizing system, UDP-glucuronosyltransferase (UGT), was additionally evaluated. The involvement of dapsone hydroxylamine (DDS-NHOH) generation in these processes was estimated by comparing the data in male and female rats since N-hydroxylation of DDS mainly occurs in males. Our studies revealed an increase in the GSSG/GSH biliary output ratio, a sensitive indicator of oxidative stress, and in lipid peroxidation, in male but not in female rats treated with DDS. The activity of all antioxidant enzymes was significantly impaired by DDS treatment also in male rats, whereas UGT activity was not affected in any sex. Taken together, the evidence indicates that DDS induces oxidative stress in rat liver and that N-hydroxylation of DDS was the likely mediator. Impairment in the activity of enzymatic antioxidant systems, also associated with DDS-NHOH formation, constituted a key aggravating factor.

TERAPÊUTICA / COMPLICAÇÕES / REAÇÕES ADVERSAS / RESISTÊNCIA

Hernandez E, Cardona-Castro N, Rodriguez GV, Sonia BC, Kimura M, Vissa VD, et al. Estudio de resistencia a la rifampicina y la dapsona en tres pacientes con recurrencia de lepra. *Rev panam salud publica* 2008; 23(2):73-7.

OBJETIVO: Detectar la presencia de cepas de *Mycobacterium leprae* resistentes a la rifampicina y la dapsona en tres pacientes con recurrencia de lepra y sospecha clínica de resistencia antimicrobiana, mediante la aplicación de técnicas moleculares. MÉTODOS: Se realizó un estudio descriptivo retrospectivo en tres pacientes multibacilares del Sanatorio de Agua de Dios, Cundinamarca, Colombia, que habían presentado recidivas de lepra documentadas por su historia clínica, baciloscopia y biopsia. Se obtuvieron biopsias de lesiones cutáneas que se procesaron para la extracción y purificación del ADN bacilar. Se amplificaron regiones de los genes *rpoB* y *folP1* asociadas con la resistencia antimicrobiana, mediante la reacción en cadena de la polimerasa "touch-down" y se secuenciaron los productos amplificados mediante el método de Sanger. RESULTADOS: Se detectó una mutación puntual en el nucleótido 1367 del gen *rpoB* en dos de las muestras estudiadas. No se encontró la mutación estudiada en el gen *folP1* en ninguno de los tres pacientes. CONCLUSIONES: La mutación identificada demostró la presencia de bacilos de *M. leprae* resistentes a la rifampicina en dos de los tres pacientes estudiados con recurrencia de la enfermedad. No se detectó la mutación indicadora de resistencia a la dapsona en ninguno de los tres pacientes.

Literatura corrente em hanseníase

Lu PH, Lin JY, Tsai YL, Kuan YZ. Corticosteroid pulse therapy for leprosy complicated by a severe type 1 reaction. *Chang Gung Med J* 2008; 31(2):201-6.

A 24-year-old Vietnamese woman presented with a 3-month history of non-itchy erythematous plaques on the face, trunk and limbs. Borderline lepromatous leprosy was confirmed by clinical findings, acid-fast bacilli on skin biopsy specimen and skin smear and a history of exposure. Around the twentieth day of World Health Organization (WHO) multibacillary standard treatment (rifampin 600 mg per month, dapsone 100 mg per day, clofazimine 300 mg per month and 50 mg per day for 1 year), she developed fever, general malaise, blurred vision, cough, nausea, epigastric pain, and arthralgia. The skin lesions also became swollen. During hospitalization, her illness was complicated by retrobulbar optic neuritis, secondary bacterial pneumonia, pleuritis, ascites, hepatitis, antral gastritis, progressive normocytic anemia, and peripheral sensory loss. The patient recovered after receiving systemic steroid pulse therapy (prednisolone equivalent dose 1250 mg) with systemic antibiotics (cefuroxime), adjustment of her anti-lepromatous therapy, and supportive care. She resumed the WHO multibacillary regimen uneventfully. This patient presented with a diverse type 1 reaction, which is a complex immune response in leprosy. We found that the judicious use of high dose steroids followed by a slow tapering course is beneficial in managing patients with a severe type 1 reaction. At the 1-year follow up, the patient had generalized skin hyperpigmentation resulted from long-term clofazimine use and numbness on feet without other systemic sequelae

Paina FA, Queiroz RH, Souza AM. Hematological, hemostatic and biochemical alterations induced by clofazimine and clarithromycin, in single and multiple doses, in rats. *Rev Soc Bras Med Trop* 2008 May-Jun;41(3):282-7.

Clarithromycin and clofazimine have been used to treat leprosy, tuberculosis and infections caused by the *Mycobacterium avium* complex. Since there is a scarcity of data on the toxicity of therapeutic regimens that

include these drugs, this study had the aim of determining the adverse effects of these therapies, through evaluation of hematological, hemostatic and biochemical parameters. The drugs were administered to male Wistar rats, as monotherapy, in regimens of single and multiple doses. Clarithromycin caused increases in the numbers of mononuclear and polymorphonuclear leukocytes. Both of the drugs inverted the proportions between mononuclear and polymorphonuclear cells and increased the numbers of polymorphonuclear cells and degenerating cells. Clofazimine and clarithromycin prolonged the prothrombin time and clarithromycin also prolonged the activated partial thromboplastin time. Clarithromycin caused increases in total and direct bilirubin. Both of the drugs increased the plasma levels of gamma-glutamyltransferase. Therefore, clofazimine and clarithromycin induce hematological, hemostatic and hepatic changes.

TERAPÊUTICA/CONTROLE

Vetrichevvel TP, Pise GA, Thappa DM. A case report of venous thrombosis in a leprosy patient treated with corticosteroid and thalidomide. *Lepr Rev* 2008 Jun; 79(2):193-5.

Thalidomide is the drug of choice in the treatment of severe erythema nodosum leprosum (ENL) in men. It has recently been associated with deep venous thrombosis (DVT) when used in treatment of refractory multiple myeloma along with combination chemotherapy. We report a case of DVT in a patient treated for ENL with corticosteroids and thalidomide, and suggest a possible mechanism for the association.

TERAPÊUTICA EXPERIMENTAL

Wiwanitkit V. Ligand-binding prediction for ErbB2, a key molecule in the pathogenesis of leprosy. *Indian J Dermatol Venereol Leprol* 2008; 74(1):32-4.

Mycobacterium leprae is an obligate intracellular pathogen. Ligand-binding is an important factor in the success of chemoprevention and chemotherapy. A new drug that can inhibit *M. leprae* binding to and activation of, ErbB2 and Erk1/2 in primary Schwann cells is the new therapeutic option. However, the ligand-binding pattern of ErbB2 has never been clarified. **METHODS:** In this work, the author performed a ligand-binding prediction for ErbB2 using a new bioinformatics tool. **RESULTS:** According to this study, nine strong possible ligands can be identified. **CONCLUSION:** These sites can be useful for further drug-development studies.

ÚLCERAS

Li J, Mu H, Ke W, Bao X, Wang Y, Wang Z, et al. The sustainability of self-care in two counties of Guizhou Province, Peoples' Republic of China. *Lepr Rev* 2008; 79(1):110-7.

This paper presents the findings of a follow-up survey conducted in two rural counties of Guizhou Province, PRC where a programme to prevent disabilities amongst leprosy affected people had been conducted. An initial 3-year programme had been conducted. One year after the final evaluation of the programme, a team was deployed to conduct a survey in the area. The objective of the survey was to establish the level of adherence to self-care. It was found that 87% of the sample of people living in leprosy villages that were surveyed ($n = 31$) and 50% of the sample of people living in general communities ($n = 50$) had continued to apply self-care. Interviews with family members suggested that 18 of the 27 self-care practising subjects living in the leprosy villages received encouragement or active support from family members (9 were single people). Twenty three of the 25 self-care practising subjects living in the communities also received family support (2 were single people). Family support was a highly significant factor influencing adherence in the community (OR = 15.8, CI = 3.0 to 83)

but it may not have been the primary motivating factor in the leprosy villages where single people were just as likely to have adhered to self-care than people who were living in families (OR 0.5, CI = 0.06 to 4.2). The prevalence of foot ulceration among that population was recorded but a hypothetical association between the prevalence of foot ulceration and self-care adherence could not be investigated due to insufficient data to address the potential effects of confounding variables. Thirty-eight percent of subjects who did not practice self-care presented with ulceration or foot cracks ($n = 29$) compared with only 25% of people who did ($n = 52$).

VACINAS

Düppre NC, Camacho LA, Cunha SS, Struchiner CJ, Sales AM, Nery JA, et al. Effectiveness of BCG vaccination among leprosy contacts: a cohort study. *Trans R Soc Trop Med Hyg* 2008;102(7):631-8.

The study assessed the effectiveness of BCG vaccination against leprosy among the contacts of 1161 leprosy patients at the FIOCRUZ Leprosy Outpatient Clinic, RJ, Brazil, from June 1987 to December 2006. Following National Leprosy Program guidelines, the clinic has administered one-to-two doses to all healthy contacts since 1991. Among the 5680 contacts, 304 (5.4%) already had leprosy. Of the 5376 eligible healthy contacts, 3536 were vaccinated, 30 of whom were excluded due to previous or current tuberculosis, or HIV. In 18 years of follow up, 122 (2.15%) incident cases were diagnosed (58 vaccinated and 64 not), 28 occurring in the first year of follow up (21 vaccinated, 16 with no scar). The protection conferred by BCG was 56% and was not substantially affected by previous BCG vaccination (50% with a scar and 59% without). The risk of tuberculoid leprosy during the initial months was high among those vaccinated with no scar. However, it had substantially declined by the first year and in the following years, when the protection rate in this group reached 80%. Since Brazil is endemic for leprosy and the detection rate is not declining satisfactorily, vaccinating all contacts could be an effective means of substantially reducing the incidence of leprosy.

Literatura corrente em hanseníase

Antas PR, Castello-Branco LR. New vaccines against tuberculosis: lessons learned from BCG immunisation in Brazil. *Trans R Soc Trop Med Hyg* 2008; 102(7):628-30.

The current tuberculosis (TB) vaccine *Mycobacterium bovis* BCG has been employed for some 70 years in Brazil and lessons from its use should be taken in account for the development or improvement of new TB vaccines. The vast majority of the current population has been vaccinated with BCG, with the possible requirement for a booster immunisation in adulthood for TB protection. BCG Moreau strain also protects against leprosy, meningitis and extrapulmonary forms of TB. Factors related to differences in strain, dosage and BCG administering protocol have been responsible for the variable efficacy of BCG. This vaccine is clearly affected by, as yet unclear, host and/or environmental variables. In this brief review, we describe some aspects of BCG immunisation observed in Brazil that may be of importance for improving or replacing BCG