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ACTIVE SEARCH FOR LEPROSY CASES IN MIDWESTERN BRAZIL: A SEROLOGICAL EVALUATION OF ASYMPTOMATIC HOUSEHOLD CONTACTS BEFORE AND AFTER PROPHYLAXIS WITH BACILLUS CALMETTE-GUÉRIN

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SUMMARY

Leprosy is a disease caused by *Mycobacterium leprae* that carries a high risk of disability, making early diagnosis mandatory. This study aimed to determine the applicability of anti-PGL-1 IgM antibody detection, using the ML FLOW technique, as an assistant tool for the detection of leprosy infection in asymptomatic household contacts (AHHC) of multibacillary leprosy index cases from Midwest Brazil. Serological changes induced by the prophylaxis of these household contacts with Bacillus Calmette-Guérin (BCG) were also verified. A total of 91 AHHC were assessed, among which, 18.68% ($n = 17$) presented both positive bacilloscopy and positive anti-PGL-1 IgM serology. Positivity concordance between these two laboratorial exams (Kappa Index = 1; $p < 0.001$) was indicated, however, one case did not demonstrate concordance between the semiquantitative assessment of anti-PGL-1 IgM and the bacilloscopy index (Kappa Index = 0.96; $p < 0.001$). Among the 17 AHHC with positive bacilloscopy, eight were reassessed after prophylaxis with BCG and two of them presented negative anti-PGL-1 IgM serology, being these patients who had presented a bacilloscopy index of < 2[+] in the initial assessment. This study shows that anti-PGL-1 IgM detection may be used as a tool to determine the bacillary load in AHHC and to detect immune changes related to prophylaxis by nonspecific vaccination.

KEYWORDS: Leprosy; *Mycobacterium leprae;* Diagnosis; Prevention & control.

INTRODUCTION

Leprosy is a chronic infectious disease that is caused by *M. leprae*, an obligate intracellular mycobacterium. Leprosy has a long incubation period and mainly affects the skin and nerves; however, a broad spectrum of clinical manifestations may be present. Early disease recognition is essential to prevent neural damage, usually associated with a late diagnosis and adverse outcomes[20].

Currently, the evaluation of household contacts of multibacillary leprosy patients is routinely conducted via clinical examination[19]. However, this approach depends on qualified human resources and is subject to variation depending on examiner experience and qualification[8]. Recent studies using sensitive laboratory techniques have demonstrated that approximately 18% of household contacts of leprosy patients may also be infected by *M. leprae* and may develop the disease[2]. This index can be as high as 50% when only the household contacts of multibacillary patients are considered[2,7]. The current approach used to prevent transmission is the early administration of multidrug therapy in multibacillary cases, since prophylaxis against leprosy is still under debate and no specific vaccine against *M. leprae* is available[20]. Passive immunization with Bacillus Calmette-Guérin (BCG) is indicated for asymptomatic contacts and offers variable levels of protection[3].

Clinical trials conducted on household contacts in order to detect new cases of leprosy are of great importance. Many clinical and laboratorial methods for the diagnosis of leprosy have been investigated. Phenolic glycolipid-1 (PGL-1) is an antigen specific to *M. leprae* that induces the formation of the IgG and IgM class antibodies[13]. PGL-1 is found in high concentrations in the serum and tissues of untreated multibacillary patients and is involved in the strong humoral response seen in patients with the lepromatous form of the disease[13].

The detection of antibodies against PGL-1 (anti-PGL-1) has been widely studied as an approach for leprosy diagnosis. When evaluating contacts of leprosy patients, anti-PGL-1 positivity has been associated with passive transmission, which is an indicator of the prevalence of the disease[7,9]. Various laboratorial techniques for the detection of anti-PGL-1 antibodies are available, although the ML FLOW method, besides being easy to implement in daily clinical practice, has shown similar sensitivity and specificity to the ELISA method when tested as a diagnostic tool in a leprosy endemic population[13].

This study aimed to determine the applicability of the ML FLOW

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technique in the diagnosis of leprosy in asymptomatic household contacts (AHHC) of multibacillary index cases from Midwestern Brazil, by means of the concordance between the ML FLOW test and bacilloscopy. A serological analysis of immune changes initiated after immunogenic stimulus with BCG vaccination was also performed.

MATERIAL AND METHODS

This study was conducted with household contacts of multibacillary leprosy patients who attended the dermatology clinic at the Brasilia University Hospital (Brazil) from March 2006 to October 2006. After each diagnosis of a patient having multibacillary leprosy, following the World Health Organization (WHO) criteria, their household contacts were actively catalogued, contacted and invited to take part in the study. The index cases were not included in this study.

All of the household contacts who agreed to participate in the study were questioned and examined by a dermatologist with regards to signs or symptoms of cutaneous or neural leprosy. Clinical examination consisted of a complete examination of the skin, nerve palpation, temperature and pain sensitivity test of extremities and any suspicious lesion. Specific neurological exams such as electroneuromyography and microfilaments tests were not employed because they are not routine screening tools and because they usually show only signs of late onset diseases. All household contacts were classified as AHHC of multibacillary leprosy index cases and finally included in the study if they lacked any signs of infection after inquiry and dermatological examination[3,20]. The intent to participate was formalized through a free and informed consent form, which was signed by all of the patients. The study is in accordance with the Helsinki Declaration, as revised in 1983.

All the selected AHHC were submitted to dermal cell scraping and blood samples collection for bacilloscopy and ML FLOW testing, respectively. Next, all the contacts received prophylaxis with one dose of BCG, in accordance with the Brazilian's Health Ministry recommendations. In addition, they were instructed to return to the dermatology clinic after approximately 30 days for a new clinical evaluation and for checking test. All those contacts who attended the 30-day follow-up visit had new samples collected if they had presented positive bacilloscopy or positive ML FLOW serology in the first samples. Resample of contacts who showed positive bacilloscopy and did not attend the follow-up visit was not performed; however, they were actively pursued by health authorities for the immediate initiation of leprosy treatment.

Dermal cell scraping samples for bacilloscopy were always collected by experienced professionals, from at least four sites, e.g. earlobes, one elbow, and one lesion. In the absence of lesions, the collection was performed in the following areas: earlobes, elbows, and knees[4]. Bacilloscopy sample analysis was performed by the Public Health's Central Laboratory at Brasilia (LACEN-DF), a public agency on behalf of the Health Secretariat of the Brazilian Federal District, which is the national reference laboratory for the analysis of this kind of samples. The sample analysis technique consisted of five steps: collection, fixation, Ziehl-Neelsen staining, microscopy, reading, and interpretation. The results were expressed on a scale that ranged from 0 to 6 according to Ridley's logarithmic scale[4].

The ML FLOW test results were recorded using qualitative (positive or negative) and semiquantitative (0[+], 1[+], 2[+], 3[+], and 4[+]) scores. Testing was carried out using a semisynthetic antigen containing natural trisaccharide linked to bovine serum albumin (natural trisaccharide-phenylpropionate-bovine serum albumin or NT-P-BSA)[5,12].

IBM® SPSS®, v.18.0, was used for the analysis of descriptive data and concordance evaluation. Also, the OpenEpi, v.2.3.1, was used to calculate sensibility, specificity, predictive and accuracy values. The statistical analysis assigned priority to the qualitative and quantitative concordance of the ML FLOW test and bacilloscopy, by using the Kappa index. The significance level was considered 5%, and the confidence interval (CI), 95%.

RESULTS

A total of 91 AHHC of multibacillary leprosy index cases were evaluated. Overall, the mean age was 32.68 ± 17.01 years; 49.45% were aged between 15 to 40 years; 15 (16.48%) were up to 15 years-old; and 25 (27.47%) were of male gender.

Among the 91 AHHC evaluated, a total of 18.68% (n = 17) patients tested positive for leprosy according to both the ML FLOW and bacilloscopy results. Regarding a qualitative analysis, there was 100% (n = 17) concordance between the tests. (Kappa Index = 1; $p < 0.001$) (Table 1). However, the tests only showed concordant quantitative results in 16 patients (Kappa Index = 0.96; $p < 0.001$). There was no quantitative correlation between tests only in one case, even though both exams resulted positive (Table 2).

Table 1
Qualitative correlation between the ML FLOW test and bacilloscopy in multibacillary leprosy contacts

ML FLOW	Bacilloscopy					
	Positive		Negative		Total	
	n	%	*n*	%	*n*	%
Positive	17	100	0	0	17	18.68
Negative	0	0	74	100	74	81.31
Total	17	100	74	100	91	100

Kappa Index = 1; Standard error = < 0.001; $p < 0.001$. Wilson Score: Sensitivity 100%(95% CI 0.81-1), specificity 100%(95% CI 0.95-1), positive Predictive Value 100%(95% CI 0.81-1), negative predictive value 100%(95% CI 0.96-1), diagnostic accuracy 100% (95% CI 0.96-1).

Most of the AHHC with positive bacilloscopy and ML FLOW were male (n = 12), and none of them were under 15 years of age. However, positivity was detected in three patients who were 15 to 25 years of age, eight patients who were 26 to 39 years of age, three patients who were 40 to 59 years of age, and three patients who were 60 years of age or more. Sensitivity (95% CI 0.81-1), specificity (95% CI 0.95-1), negative (95% CI 0.96-1) and positive (95% CI 0.81-1) predictive values, and diagnostic accuracy (95% CI 0.96-1) of ML FLOW test were complete (100%), although there was no statistical significance.

Although there was no clinical signs of leprosy, the AHHC who

Table 2
Correlation of the results of the semiquantitative ML FLOW test and the bacilloscopy index in contacts: number of patients

Bacilloscopy index	ML FLOW					Total
	0	[+]1	[+]2	[+]3	[+]4	
0	74	0	0	0	0	74
1[+]	0	9	1	0	0	10
2[+]	0	0	3	0	0	3
3[+]	0	0	0	2	0	2
4[+]	0	0	0	0	2	2
5[+]	0	0	0	0	0	0
6[+]	0	0	0	0	0	0
Total	74	9	4	2	2	91

Kappa Index = 0.96; Standard error = 0.033; $p < 0.001$.

presented positive skin smears were classified as multibacillary leprosy patients according to WHO recommendations[20]. From the 17 household contacts with positive results, only eight attended the 30-day follow-up visit and underwent a resample collection. For all these patients, the new bacilloscopy results were 100% consistent with first sample results. However, new ML FLOW testing revealed only six patients maintained positive results (patients presenting initial BI greater than 2[+]), and two patients with negative results (patients presenting initial BI lower than 2[+]). (Kappa Index = 0.86; $p < 0.001$) (Table 3). All the 17 multibacilary AHHC received treatment prescription for multibacillary leprosy after the first follow-up visit or after active search realized by local health authorities.

Table 3
Serological evolution and bacilloscopy evaluation in contacts of patients with multibacillary leprosy before and after vaccination with BCG

Patient	Pre-BCG vaccination		Post-BCG vaccination	
	IB	ML FLOW	IB	ML FLOW
1	≥2 [+]	[+]	≥2 [+]	[+]
2	≥2 [+]	[+]	≥2 [+]	[+]
3	≥2 [+]	[+]	≥2 [+]	[+]
4	≥2 [+]	[+]	≥2 [+]	[+]
5	≥2 [+]	[+]	≥2 [+]	[+]
6	≥2 [+]	[+]	≥2 [+]	[+]
7	<2 [+]	[+]	<2 [+]	[-]
8	<2 [+]	[+]	<2 [+]	[-]

Kappa Index = 0.96; Standard error = 0.082; $p < 0.001$.

DISCUSSION

Leprosy is a disease of insidious progression, which makes its detection difficult, particularly in patients with the lepromatous form. An infected patient can maintain the status of being a transmitter of leprosy for years before presenting any recognizable clinical sign[2,8]. Thus, strategies aiming for the early diagnosis of leprosy are of great importance. The use of isolated clinical examinations as a tool to early identify multibacillary patients is frequently subject of discussion[8,14]. Many new approaches have been employed with the aim of improving the diagnosis sensitivity and for optimizing the detection of multibacillary patients as well as in household contacts[13].

Studies on ML FLOW testing have focused on the detection of new cases, principally among contacts, with the goal of endemic control[8]. The Brazilian Midwest is an endemic area for leprosy; therefore, epidemiological research that assesses the risk of contagion to the local population is of great value in determining surveillance policies. This study detected an 18.68% positive bacilloscopy and seropositivity among AHHC of multibacillary leprosy patients. Such a rate is comparable to that found in other Brazilian regions[10].

The expressive amount of household contacts presenting no symptoms at clinical examination, even those who tested positive to anti-PGL-1 antibodies, surely emphasizes the limitations of the isolated clinical examination in the detection of leprosy cases, even multibacillary ones. This current study relied on clinical examination performed by dermatologists specialized in leprosy management working in a tertiary hospital, nevertheless clinical diagnostic failure was as high as reported. Otherwise, it must be stressed that in Brazil, the evaluation of contacts is mostly made at primary care institutions and often by professionals without medical formation, which may worsen the efficacy of the clinical examination[17].

Clinical signs of leprosy are usually a result of the body immune response. This fact may help explain the lack of clinical recognition of the 17 multibacillary AHHC of our study, since these patients show a Th2 bent immune response that may not be sufficient to fight the infection. These patients may present a long time of bacilli proliferation before recognizable clinical signs, even to trained eyes of specialists.

In our study we evaluated only AHHC of multibacillary index cases. However, due to data limitations, we could not evaluate the rate of consanguinity between household contacts and index cases. Considering in-house transmission, we may expect a high rate of linear and collateral consanguinity between them. This information may also support the occurrence of higher rates of multibacillary disease among household contacts of multibacillary index cases, since they may share a similar specific immune response to leprosy, determined by the consanguinity relationship[2].

ARAÚJO (2003) and other contemporary authors have demonstrated a directly proportional correlation between the intensity of ML FLOW test results and the bacillary load, especially among lepromatous patients[1]. These results demonstrate anti-PGL-1 serology as a good indicator of the bacillary load[1,6,11,13,15]. These findings are consistent with the data from literature showing anti-PGL-1 IgM positivity close to 100% in multibacillary cases[12,13]. These individuals classically exhibit an immune response that favors the Th2 pathway, which is usually insufficient for the destruction of the bacillus. Immune response in multibacillary disease determines the formation of high titers of antibodies, being the bacilloscopy and serological tests usually with concurrently positive results.

The negative trend of the ML FLOW results after BCG prophylaxis could have resulted from a more balanced immune response presented by the two patients presenting reduced bacillary loads (<2[+]). TABOURET *et al.* (2010) consider that the lipid constituents of *M. leprae* envelope are structurally similar to those of *M. bovis* BCG, except PGL[18] The same group reprogrammed the PGL biosynthesis pathway in *M. bovis* BCG. They stated that the construction of recombinant BCG producing PGL-1 augments its infectivity and intracellular growth in human macrophages[18]. Therefore, the immune stimulus triggered by BCG without PGL-1 antigens may have stimulated Th1 response, which caused a decrease in the anti-PGL-1 IgM titers and a negative trend in the results. Otherwise, the short time (30 days) for retesting surely was not sufficient for a negative trend in bacilloscopy. Ultimately, the ML FLOW result changes could be explained by a sensitivity variation inherent of any diagnostic test. Unfortunately, a qualitative bacillary evaluation was not performed on the second samples to estimate the bacilli viability in these patients. Several studies relate the reduction of anti-PGL-1 IgM antibodies to a decrease in bacillary antigenic stimulus and a transmission chain break[9,16], which in our patients could have resulted from a smaller load of viable bacilli secondary to Th1 immune response activation.

Data from the Brazilian Leprosy Control Program showed that after the identification of leprosy index cases in the period of 2001 to 2007, only 50.6 % of their household contacts were submitted to a clinical examination[17]. This means that almost half of the contacts are not evaluated due to operational failures. Furthermore, many contacts, even multibacillary, may not be diagnosed after specialist's evaluation due to the lack of recognizable clinical signs. Together, this data calls for the implementation of more suitable measures of surveillance, other than the clinical examination, which could promote easier and more effective identification of transmission sources. To change the actual scenario, the adoption of new diagnostic techniques seems imperative. It would allow for the early detection of multibacillary cases and prophylaxis, even in areas with persistence of small transmission foci, in countries where leprosy is virtually considered to be controlled[8].

This study is in accordance with previous data which shows the effectiveness of the ML FLOW test in the detection of multibacillary disease among asymptomatic contacts of multibacillary patients. The method demonstrated concordance with and a similar sensitivity to bacilloscopy. Therefore, we believe that the ML FLOW test is an approach that can assist in the diagnosis and classification of leprosy cases in high-risk groups and in populations with a high prevalence, as previously recommended by other authors[12]. Prophylaxis with BCG is not specific for *M. leprae,* although it has been shown effective in modulating the immune response in several patients, and may reduce the number of patients who transmit the disease. This immune modulating role of BCG vaccination was probably the main stain for the changes on serology status of our patients, although new studies are necessary to confirm our findings.

RESUMO

Busca ativa por casos de hanseníase no Centro-Oeste do Brasil: avaliação sorológica dos contatos domiciliares assintomáticos antes e após a profilaxia com Bacillus Calmette-Guérin

A hanseníase é doença causada pelo *Mycobacterium leprae*, apresentando elevado potencial incapacitante, o que torna indispensável seu diagnóstico precoce. O estudo visa determinar a aplicabilidade da detecção de anticorpos anti-PGL1-IgM por meio da técnica do ML FLOW como ferramenta adjuvante ao diagnóstico de hanseníase em contatos domiciliares assintomáticos (AHHC) de pacientes multibacilares procedentes da região Centro-Oeste do Brasil, bem como, documentar o comportamento sorológico após a profilaxia com a vacina Bacillus Calmette-Guérin (BCG). Foram avaliados 91 AHHC atendidos no Hospital Universitário de Brasília - Brasil, dos quais 18,68% ($n = 17$) apresentaram positividade para baciloscopia e anti-PGL1-IgM, totalizando uma concordância completa entre os dois grupos (Índice Kappa = 1; $p < 0,001$). Em apenas um dos casos não observou-se concordância entre a avaliação semi-quantitativa do anti-PGL1-IgM e índice baciloscópico (Índice Kappa = 0,96; $p < 0,001$). Oito dos 17 AHHC com baciloscopia positiva foram reavaliados após profilaxia com BCG e apenas dois apresentaram negativação dos títulos anti-PGL1-IgM, sendo tais casos correspondentes aos que haviam apresentado índice baciloscópico menor do que 2[+] na avaliação inicial. O estudo corrobora o potencial do anti-PGL1-IgM como ferramenta de predição da carga bacilar em AHHC da região Centro-Oeste do Brasil, e surpreende alterações imunes relacionadas à profilaxia obtida pela vacinação não específica com BCG.

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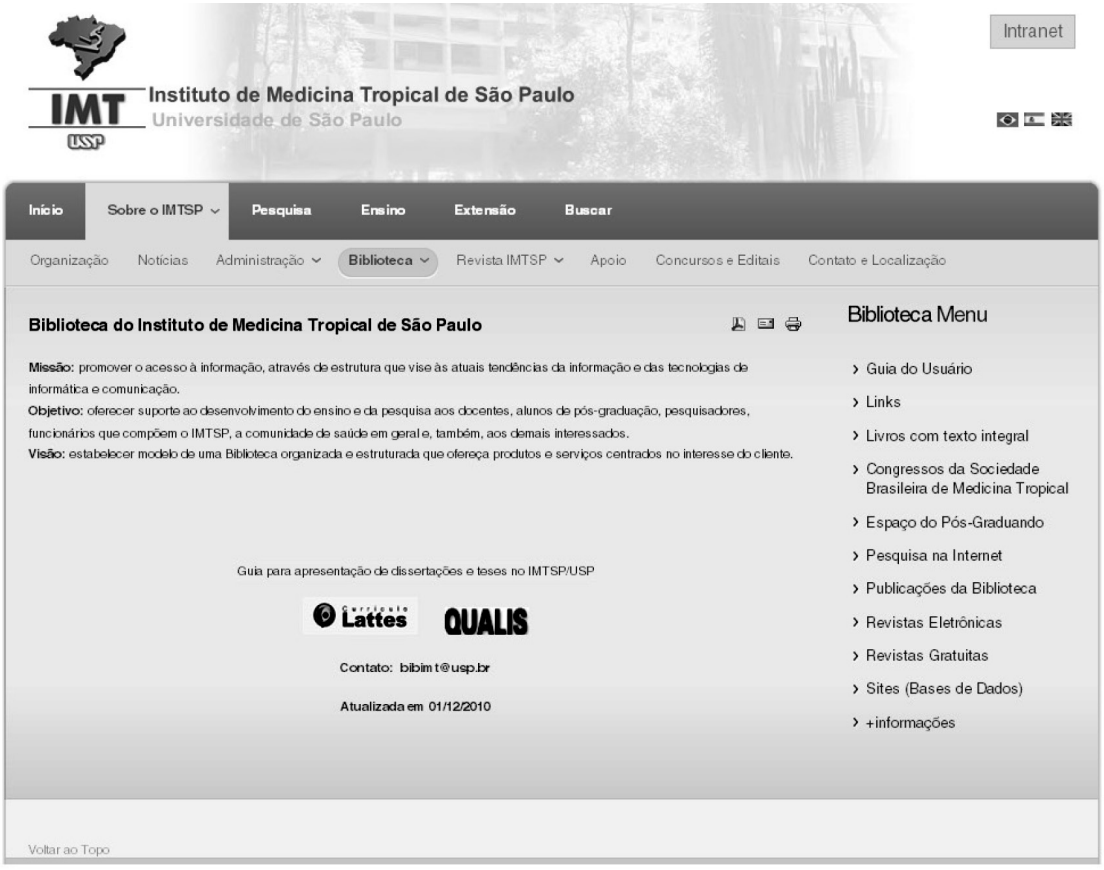

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