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THE USE OF THE ML FLOW TEST BETWEEN NEWLY DIAGNOSTIC LEPROSY CASES AND IN-HOME CONTACTS

O uso do teste MI flow entre casos de hanseníase recém-diagnosticados e contatos intradomiciliares

El uso de la prueba de flujo MI entre casos de lepra recientemente diagnósticos y contactos en el hogar

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ABSTRACT

Objective: to identify the MI Flow test result between newly diagnosed leprosy cases and household contacts. **Methods:** cross-sectional, descriptive study with a quantitative approach carried out in the city of Caxias, Maranhão, Brazil, where newly diagnosed cases, treatment virgins and intra-household contacts were recruited. **Results:** 324 contacts of leprosy cases were recruited from 2015 to 2018. In newly diagnosed cases, the MI Flow test was negative in 87.5% (7/8) of paucibacillary patients and positive in 70% (21/ 30) of the multibacillary, both in agreement with the bacilloscopy of the intradermal smear. Thirty (9%) household contacts with high risk of illness were identified. **Conclusion:** the MI Flow test is a useful tool for the correct detection of contacts with a high chance of getting sick from leprosy, as well as for correctly classifying new cases.

DESCRIPTORS: Serological tests; Communicable diseases; Neglected diseases.

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RESUMO

Objetivo: identificar o resultado de teste *Ml Flow* entre casos de hanseníase recém-diagnosticados e contatos intradomiciliares. **Métodos:** estudo transversal, descritivo, com abordagem quantitativa realizado no município de Caxias, Maranhão, Brasil, onde recrutou-se casos recém-diagnosticados, virgens de tratamento e contatos intradomiciliares. **Resultados:** recrutou-se 324 contatos de casos de hanseníase, no período de 2015 a 2018. Nos casos recém-diagnosticados o teste *Ml Flow* foi negativo em 87,5% (7/8) dos paucibacilares e positivo em 70% (21/30) dos multibacilares, ambos concordantes com a baciloscopia do raspado intradérmico. Identificou-se 30 (9%) contatos intradomiciliares com alto risco de adoecer. **Conclusão:** o teste *Ml Flow* constitui-se uma ferramenta útil para correta detecção de contatos com alta chance de adoecer da hanseníase, bem como para classificar corretamente os casos novos.

DESCRITORES: Testes sorológicos; Doenças transmissíveis; Doenças negligenciadas.

RESUMEN

Objetivo: identificar el resultado de la prueba Ml Flow entre casos de lepra recién diagnosticados y contactos domésticos. **Métodos:** estudio descriptivo transversal con abordaje cuantitativo realizado en la ciudad de Caxias, Maranhão, Brasil, donde se reclutaron casos recién diagnosticados, vírgenes en tratamiento y contactos intrafamiliares. **Resultados:** se reclutaron 324 contactos de casos de lepra entre 2015 y 2018. En los casos recién diagnosticados, la prueba Ml Flow fue negativa en el 87,5% (7/8) de los pacientes paucibacilares y positiva en el 70% (21/30) de los multibacilares, ambos de acuerdo con la baciloscopia del frotis intradérmico. Identificamos 30 (9%) contactos dentro del hogar con alto riesgo de enfermarse. **Conclusión:** la prueba Ml Flow es una herramienta útil para la correcta detección de contactos con alta probabilidad de enfermarse de lepra, así como para clasificar correctamente nuevos casos.

DESCRITORES: Pruebas serológicas; Enfermedades contagiosas; Enfermedades desatendidas.

INTRODUCTION

In global health agendas, there is an understanding of neglected diseases as those that more strongly affect historically vulnerable populations (exposed to precarious sanitary structures, housing and food conditions, and difficulty in accessing the health system) and that attract low volume of resources from countries and companies.[1]

Leprosy is a neglected disease that, despite being treatable, presents high risk for disabilities and severe deformities throughout life due to delays or misdiagnoses, constituting a public health problem, especially in developing countries.[2] The identification of signs and symptoms of the disease together with an early diagnosis are important for its effective control, such actions reduce transmission, especially among household contacts, and consequently prevent physical disabilities.[3]

The etiologic agent of leprosy is Mycobacterium leprae, which, taxonomically, belongs to the order Actinomycetales and family Mycobacteriaceae; it consists of an obligate intracellular parasite, predominant in macrophages, where it can be observed forming clusters or globules in parallel arrangements. It remains alive for up to ten days at 4°C; outside the human body, in nasal secretions, it survives for up to seven days at 20°C.[4]

The disease has a long incubation period, an average of 2 to 5 years, due to the slow growth and multiplication of M. leprae, manifesting itself with dermatoneurological lesions that affect mainly the integument and the peripheral nervous system. Man is considered the most important source of leprosy infection, and its transmission results from exposure to the bacillus through the upper airways of a sick person by its infectious forms, without treatment, which eliminates the bacillus to the external environment, infecting susceptible exposed people through intimate and prolonged contact, very common in household cohabitation.[5-6]

The diagnosis of leprosy cases is essentially clinical and epidemiological, carried out by means of anamnesis, general examination, and dermatoneurological examination. The operational classification, in order to determine the most effective treatment, is based on Paucibacillary (PB) – cases with up to five skin lesions, in which patients have low bacilli counts and, therefore, do not transmit the disease, presenting in the Indeterminate and Tuberculoid forms; Multibacillary (MB) – cases with more than five skin lesions, in which patients have high bacillary load due to the inability of the immune system to neutralize the microorganisms, have a higher potential for transmissibility, and are presented in the Dimorphic and Virchowian forms.[7-8]

Laboratory tests such as intradermal smear microscopy, histopathology, Mitsuda reaction and serology can be used to assist in the correct classification of cases.[9] However, currently, skin smear microscopy is the most used complementary test in the diagnostic investigation of leprosy because it identifies the causative agent, but it is negative in the PB and some MB forms.[10]

Leprosy is an infectious disease that does not have a gold standard test for its diagnosis because M. leprae does not reproduce in vitro culture media, so in the search for diagnostic options, several methods have been proposed. In 2003, a simple and rapid lateral flow immunochromatographic test, Ml Flow, was developed for the detection of IgM against phenolic glycolipid I (PGL-I), a specific antigen of M. leprae, and results are obtained within 5 to 10 minutes using whole blood or serum. It does not require a specific laboratory and refrigeration, and can be used

as an auxiliary tool to classify patients for treatment purposes in Basic Health Units (BHU).[10]

Studies indicate that serology is more sensitive than sputum smear microscopy and that it can be used in the classification of leprosy cases in PB and MB, as well as having the potential to identify among contacts those at higher risk of developing leprosy.[11] The aim of this study was to identify the Ml Flow test results among newly diagnosed leprosy cases and household contacts.

METHOD

In Brazil, leprosy presents high numbers of cases, in 2015 there were 28,761 new cases. The state of Maranhão is considered hyperendemic for leprosy, this state recorded more cases than eight of the 14 countries in the world with the greatest magnitude of the disease. Its detection coefficient was 51.27/100,000 inhab. in 2015, where 3,540 new cases were registered in the year, corresponding to 13.4% of the total cases in the country. Maranhão presents a hyperendemic pattern for most of its regions.[12]

This is a cross-sectional, descriptive study with a quantitative approach. The study was conducted in the municipality of Caxias, in the state of Maranhão, this in the period from 2010 to 2014 notified 301 cases of leprosy in the 12 Basic Health Units with the highest number of cases in the municipality. For an estimated 1204 household contacts, only 45% were evaluated by the Family Health Teams.

To determine the sample size (n) based on the estimated population proportion in the municipality, we used the formula for sample calculation. The estimated sample was 244, comprised of index cases of leprosy and household contacts notified in the period from 2015 to 2017 according to information contained in SINAN Net (Sistema de Informação de Agravos de Notificação).

After the active search for leprosy cases reported in the triennium 2015-2017, in addition to new cases that were not submitted to treatment, we also searched for household contacts. We recruited 375 participants, distributed among 82 index cases (already treated), 324 household contacts and 38 newly diagnosed cases. Inclusion criteria were residing in the study municipality, being a newly diagnosed leprosy case between January 1, 2015 and December 31, 2017, age between 5 and 100 years. New cases with previous treatment for leprosy were excluded.

For data collection, 82 medical records were evaluated with the collaboration of nurses and Community Health Agents (CHAs). After this evaluation, two home visits were made, the first with the participation of the CHA for the knowledge and acceptance by the participant, and the second for those who agreed to participate in the study, where the anamnesis was made with a script of contact information that included socio-demographic variables, dermatoneurological evaluation, vaccination history with Bacillus Calmette Guérin (BCG) and the result of the Ml Flow test.

Contacts of included MB and PB patients were examined and tested with the Ml Flow, even those without clinical signs and symptoms of leprosy. The newly diagnosed cases were recruited according to the demand from the Center for Specialization in Maternal and Child Care (CEAMI) and UBS and submitted to the script for filling in the patient's data and application of the Ml Flow test.

The Ml Flow test is composed of a nitrocellulose detection strip that at one end contains the human IgM antibody labeled with dry colloidal gold and at the other end an absorption pad, a semi-synthetic trisaccharide similar to PGL-I, bound to human albumin, is used as antigen in a 1 mm line on the strip surface. Parallel to this line, human IgM conjugate is used as a reagent control. The Ml Flow reaction occurs when a blood or serum sample is placed in the sample container and is loaded with sample fluid, the reagent binds to the IgM in the blood or serum. If the antibody is specific it will bind to the PGL-I antigen and a red line will appear in the test zone. Otherwise only the control line will appear positive.[13]

The protocol for performing the Ml Flow test consists of using 5 μL of heparinized whole blood samples and adding 130 μL of buffering solution.[13] After collection, the material is deposited into the Ml Flow test sample receptacle. After 5 minutes, the result is read visually, the negative result is indicated by the absence of a line in the test range and the presence of a line in the control range, and the positive result is indicated by the presence of two lines: one in the test zone and one in the control zone, recorded in its quantitative form, 1 +, 2 +, 3 + and 4 +.

The software used for data tabulation was Microsoft Excel version 2016, where the questionnaire data were typed and frequency calculations, means and medians of the variables were performed to prepare and analyze the results.

The project was submitted to the Research Ethics Committee (CEP) of the Maranhão State University – UEMA, and all the recommendations of Resolution No. 466/2012 of the National Health Council were followed, where it was evaluated and approved on August 14, 2017, according to opinion No. 2217143. Individuals under 18 years of age who agreed to participate in the study signed the Informed Consent Form and those over 18 years of age who agreed to participate signed the Informed Consent Form – ICF, authorizing the use of biological material for research.

RESULTS

A total of 82 medical records of cases with completed treatment and under treatment for leprosy in the period between 2015 and 2017 were evaluated, as well as 38 newly diagnosed cases. Of these, 324 household contacts were surveyed. Of the participants who progressed to cure according to the operational classification 80.4% (66/82) were MB patients, according to the clinical form, the Dimorphic form was predominant in 46.3% (38/82), followed by Virchowian with 25.6% (21/82), Table 01.

We surveyed the social demographic data of the contacts submitted to the Ml Flow test and 73.7% (239/324) were over 18 years of age, 61.79% (200/324) said they were mixed race,

61.1% (198/324) were female. The predominant education level of the contacts was between 5 and 9 years of school with 30.5% (99/324). Fifty-three percent (171/324) of contacts were not immunized with the Bacille Calmette-Guérin (BCG) vaccine, a fact that deserves to be highlighted, since immunization is indicated for contacts of leprosy cases because it provides them with significant protection. Most contacts in relation to the degree of kinship, 28% (91/324) were children and/or spouses (44/324) of these patients, Table 02.

In a total of 324 contacts, 22.5% (73/324) were contacts of PB cases and 77.5% (251/324) of MB cases. Of the contacts with positive Ml Flow test, 6 (8.2%) of 73 cases were contacts of cases classified as tuberculoid or indeterminate and 9.6% (24/251) were contacts of cases classified as dimorphic or virchowian. In the analysis of the cases of contacts with positive Ml Flow it was found that in six cases (20%) six out of 30 cases the index case was PB and in 80% (24/30) the index case was MB, Table 03.

A total of 38 newly diagnosed cases were subjected to Ml Flow testing. Positive tests were more common in MB cases with 70% (21/30) of the cases. Eight (12.5%) of 30 PB cases had a positive Ml Flow test. As for the clinical form, the newly diagnosed patients had a positive Ml Flow test in the virchowian form, 100% (18/18), and a total of one (100%) case in the tuberculoid form was negative for the serological test, Table 04.

DISCUSSION

Regarding the operational classification of cases diagnosed between 2015 and 2017, 80.4% were classified as MB, and of these, 46.3% had the dimorphic form. This result does not differ from other studies that profiled leprosy patients.[14-15] This high rate of MB cases is indicative of late diagnosis.

Most patients can be diagnosed by lesions with decreased sensitivity, but some MB patients at the beginning of the disease do not manifest lesions for early diagnosis, making it difficult and sustaining the chain of transmission. This transmission can relapse in household and social contacts four to ten times higher

Table 01 – Clinical characteristics of leprosy cases in the period from 2015 to 2017, Caxias, Maranhão, Brazil, 2018

Operational Classification	N=82	%
Paucibacillary	16	19,5
Multibacillary	66	80,4
Clinical form		
Undetermined	10	12,1
Tuberculoid	6	7,3
Dimorph	38	46,3
Virchowian	21	25,6
Neural	2	2,4
Unclassified	5	6

Source: Field research, Caxias-MA, 2018

Table 02 – Clinical, social and demographic characterization of the household contacts of leprosy cases in the period from 2015 to 2017, Caxias, Maranhão, Brazil, 2018

Variable	N=324	%
Age		
<18 years old	85	26,2
>18 years old	239	73,8
Color		
White	39	12
Brown	200	61,8
Black	85	26,2
Gender		
Male	126	39
Female	198	61
Education		
Illiterate	27	8,3
Up to 4 years	63	19,5
Between 5 and 9 years old	99	30,5
Between 10 and 12 years old	92	28,4
>12 years	43	13,3
Vaccine scar BCG		
No scar	171	53
A scar	44	13
Two scars	109	34
Degree of kinship		
Mother	28	8,6
Father	12	4
Brother (sister)	39	12
Son	91	28
Nephew	26	8
Uncle	05	1,5
Spouse	44	13,5
Grandson	45	14
Cousin	07	2,1
Brother-in-law	08	2,4
Son-in-law	06	1,8
Other	13	4,1

Source: Field research, Caxias-MA, 2018.

Table 03 – Performance of the Ml Flow test in household contacts according to the operational classification of leprosy index cases in the municipality of Caxias-MA, Brazil, 2018.

Teste Ml Flow	Paucibacillary		Multibacillary	
	N=73	%	N=251	%
Negative	67	91,8	227	90,4
Positive	06	8,2	24	9,6

Source: Field research, Caxias-MA, 2018.

Table 04 – Performance of the Ml Flow test in newly diagnosed cases reported from 2017 to 2018, in the municipality of Caxias-MA, Brazil, 2018

| | Ml Flow Test | | | |
| | Positive | | Negative | |
	N	%	N	%
Operational Classification				
PB	1	12,5	7	87,5
MB	21	70	9	30
Clinical form				
Tuberculoid	0	0	1	100
Undetermined	1	14,3	6	85,7
Dimorph	3	25	9	75
Virchowian	18	100	0	0

Source: Field research, Caxias-MA, 2018.

due to MB cases, being an important link for the progression of the transmission chain; the household contacts of untreated PB cases are twice as likely to acquire the disease.[16]

One of the pillars of control measures is precisely the surveillance of contacts. Recent studies with contacts argue that their approach depends on a rigorous clinical evaluation, which allows early detection and prevention of deformities and disabilities.[17]

The use of sensitive laboratory techniques, such as the Ml Flow test, a less invasive method than the intradermal smear smear, is able to detect circulating antibodies against the PGL-I of M. leprae in contacts, besides providing less discomfort to the patient.[12,15,18-20]

In the sample of household contacts in this study there is a predominance of females, this data is linked to the fact that in the municipality where the study was conducted, data from the last IBGE Census in 2010, for samples related to population characteristics, there is a higher proportion of females, with 80,091 thousand inhabitants, while the number of men was 75,111 thousand inhabitants. This data differs from the study by Sousa et al,[21] in which the highest occurrence is associated with males due to greater exposure to work-related activities, low demand for health services, low level of self-care, and late diagnosis in this population.

As for BCG vaccination, we found that 53% of contacts were not immunized by the vaccine, but 13% had a vaccination scar and were seropositive for the Ml Flow test; this finding agrees with the literature, where most positive contacts for the Ml Flow test had a single BCG scar.[12,21] The efficacy of BCG has been demonstrated as a protective agent for leprosy among household contacts.[22] Despite the protection conferred by the BCG vaccine, studies show that contacts positive for PGL-I have been found, indicating the presence of subclinical infection, in the first months after vaccination in contacts of cases with late diagnosis.[23]

The positivity of the Ml Flow test regarding the operational classification was higher in contacts of MB cases with 80%, only 20% of contacts of PB cases had a positive test. These data explain that the high number of MB contacts positive for antibodies against PGL-I is linked to the high bacillary load, which is responsible for sustaining the chain of transmission. Studies show that the positive test result was higher for those contacts of MB cases, revealing that it is a useful tool to detect those at higher risk of becoming ill.[20-21,24]

In the study by Douglas et al[25] monitoring household contacts of leprosy patients, approximately one MB case contact from 7 families developed the disease, and the positivity rate was higher among contacts living in the same household as leprosy cases.

Importantly, during the course of this investigation, one PB case contact was diagnosed with PB leprosy. Although serology is not a universal marker for PB disease, since MB patients make up the main source of infection, it is helpful in finding patients with lower bacterial loads that are missed on skin smears, and in need of further investigation, it is hypothesized that cases that sustain transmission in some families go undiagnosed.

The cellular immune response and the degree of proximity of contact with the index case are risk factors for becoming ill. The presence of antibodies against PGL-I in contacts increases 7.2 times the chance that they will develop MB or PB leprosy, and the detection of antibodies against PGL-I indicates infection present without clinical signs in contacts, and is an important marker for screening positive contacts with the potential to develop the disease.[26] Therefore, anti-PGL-I serology may be useful as a test to detect IgM antibodies, helping in the early screening of those contacts at higher risk of becoming ill.

Samples with the presence of PGL-I antigen is an indication of current infection by M. leprae; therefore, studies have shown that patients with low bacterial index, the presence of PGL-I was detected in their samples, where 89.3% of these were virchowian MB patients and 3.7% tuberculoid PB patients with the presence of active infection in the organism.[26] Thus, an early detection method of people with a tendency to develop the most infectious form of leprosy can contribute to break the chain of transmission.

Therefore, in this study, the Ml Flow test presented results in agreement with other studies and compared to other diagnostic methods. The Ml Flow was positive in 70% of the MB index cases; this finding is close to the result obtained by a study that observed the agreement between the Ml Flow test and lymph smear microscopy to analyze the usefulness of the Ml Flow test in the field, included 55 patients, and obtained Ml Flow test positivity in 82.5% of the MB cases.[27]

The positivity ratifies that the test is sensitive for the correct classification of MB cases. To evaluate the agreement between clinical and laboratory tests in the diagnosis of leprosy, the Ml Flow test proved to be important for the correct classification of leprosy and those classified as MB with a negative test were reclassified as PB, that is, the test was positive in 71.2% (74/104) of MB.[14,28]

CONCLUSÃO

In order to identify household contacts and newly diagnosed leprosy cases with positive Ml Flow test results in the municipality of Caxias, MA, we reached a sample of 362 participants. Of these, 324 were household contacts of cases and 38 were new cases recently diagnosed and not requiring treatment. In this sample 9.3% of contacts and 57.9% of cases had a positive MI flow test.

The Ml Flow test performance in the evaluation of cases was positive in 70% of the multibacillary cases. To verify the results of the Ml Flow test in the evaluation of household contacts who are at greater risk of developing the disease, we found that 8.2% of paucibacillary contacts and 9.6% of multibacillary contacts had a positive Ml Flow test.

The Ml Flow test proved significant for the correct classification of patients with high bacillary load (multibacillary). Therefore, the use of anti-PGL-1 serology by health services could also help in the early identification of contacts at high risk for infection and adequate treatment, collaborating in the identification of the source of infection.

THANKS

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