Risk factors for ML Flow seropositivity in leprosy patients

Fatores de risco para a soropositividade do ML Flow em pacientes com hanseníase

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ABSTRACT

The early diagnosis of leprosy, its correct classification and the risk factors related to seropositivity have become important for patient treatment and disease control, especially where the responsibility for treatment has been transferred to basic health care centers. This descriptive, exploratory study using logistic regression was undertaken to evaluate the association between the variables of sex, age, mode of detection, number of skin lesions and affected nerves, disability grade and bacilloscopy with the results of the ML Flow serological test in 1,072 new leprosy cases in 13 municipalities in Minas Gerais State. Seropositivity (50.7%) was statistically associated with patients 15 years-old or over (OR:2.6) and those with more than five skin lesions (OR:7.5), more than one affected nerve (OR:2.4) and a positive bacilloscopic index (OR:5.5 for 0<BI<2 and OR:191.2 for BI≥2), thus contributing to the appropriate classification and treatment of patients.


RESUMO

O diagnóstico precoce da hanseníase, a correta classificação e o estudo dos fatores de risco relacionados à soropositividade, tornam-se importantes para o tratamento do doente e controle da endemia, especialmente, quando a responsabilidade pelo atendimento desses pacientes está sendo absorvida pelos serviços de atenção básica. Estudo descritivo e exploratório utilizando regressão logística avaliou a associação das variáveis: sexo, idade, modo de detecção, número de lesões cutâneas e de nervos acometidos, grau de incapacidade, baciloscopia, com o resultado do teste sorológico ML Flow, em 1.072 casos novos com hanseníase em 13 municípios de Minas Gerais. A soropositividade (50,7%) estava estatisticamente associada aos pacientes com 15 anos ou mais de idade (OR:2,6), mais de cinco lesões cutâneas (OR:7,5), mais de um nervo acometido (OR:2,4) e com baciloscopia positiva (OR:5,5 para IB<2 e OR:191,2 para IB≥2), colaborando, assim, com a classificação e o tratamento adequados dos doentes.


Leprosy is an infectious chronic disease caused by Mycobacterium leprae, a bacillus with a predisposition for peripheral nerves and skin, and although it does not represent a primary cause of death, it stands out among diseases that lead to disabilities1 15 19 33. Its clinical signs are typical, thus making its diagnosis simple in the majority of cases, but in others it can be confused with other neuropathies and dermatoses1.

The different clinical manifestations of leprosy are related to the immune response of the host organism17. Genetic factors and contact with other microorganisms in the surrounding environment can modify this response12.

Significant differences have been noted in leprosy detection among men and women. It is customary for men to present with more severe forms of the disease and suffer more disabilities, while women tend to have a more intense immunological response to Mycobacterium leprae and are less often diagnosed with multibacillary (MB) forms or with severe disabilities21 24. Another factor may be related to the fact that health professionals do not examine women as thoroughly as they do men, due to cultural difficulties21.

The progressive reduction in the difference between the sexes in the detection of leprosy cases has been explained by the increased presence of women in the workforce after 1960, or by increased access for women to basic health services21 24.
Leprosy is a disease that occurs in young and middle-aged adults, with a higher number of cases registered in the age group from 20 to 50 years. The appearance of leprosy in those under the age of 15 indicates early exposure to the etiologic agent, determined by a higher level of endemicity.

Evaluation of the disability grade must be conducted for the eyes, hands and feet at diagnosis and at the time of release from treatment and is an essential step in the planning of prevention of disabilities (PoD) interventions. The percentage of grade 2 disabilities or deformities among newly diagnosed and evaluated cases is defined as an important epidemiological indicator for judging the effectiveness of early leprosy detection activities, as well as estimating the existence of an undetected caseload.

Bacilloscopy is the most useful auxiliary exam for diagnosis. It is relatively easy and inexpensive to conduct, although it does require trained professionals and a laboratory, not always present in basic health care centers. The slit skin smear is collected from the lesions suggestive of leprosy, as well as the earlobes and elbows. Staining is performed according to the Ziehl-Neelsen method and the results are recorded in the form of the Bacilloscopic Index (BI) on a scale of 0 to 6+, as proposed by Ridley. The bacilloscopic reading is negative for paucibacillary (PB) patients (indeterminate and tuberculoid on the Madrid scale) and strongly positive in lepromatous patients, while variable for borderline cases. Slit skin smears are highly specific, but not very sensitive, given that approximately 70% of all leprosy patients have a negative bacilloscopic outcome.

Since 2000, the World Health Organization (WHO) has recommended a simplified method of leprosy classification and treatment based on skin lesion counts. This guideline, adopted by the Brazilian Ministry of Health in 2002, states that patients with as many as five skin lesions are classified as PB, and those with six or more lesions are multibacillary (MB) (indeterminate and tuberculoid on the Madrid scale) and strongly positive in lepromatous patients, while variable for borderline cases. Slit skin smears are highly specific, but not very sensitive, given that approximately 70% of all leprosy patients have a negative bacilloscopic outcome.

This descriptive, exploratory study compared ML Flow serological test results with the covariables of sex, age, mode of detection, number of skin lesions and affected nerves, disability grade and bacilloscopy with the results of the ML Flow serological test in 1,072 new leprosy cases. The research was undertaken by the State Health Secretariat of Minas Gerais and comprised part of a multicentric study in Brazil, Nepal and Nigeria, as coordinated by the Biomedical Research Department, Royal Tropical Institute, Amsterdam and financed by Netherlands Leprosy Relief, Amsterdam. It was approved by the Research Ethics Committees of the Santa Casa de Misericórdia in Belo Horizonte on Nov. 22, 2001, protocol no. 39/01 and of the Federal University of Minas Gerais, on Feb. 16, 2004, protocol no. 312/04. All research subjects agreed to participate and signed free informed consent forms.

Research was conducted between October 2002 and March 2004 in 14 health centers in 13 priority municipalities in Minas Gerais. The breakdown of these health centers was as follows: eight municipal health centers, four regional referral centers and two state referral centers.

The ML Flow serological test was performed as described by Bühler-Sékula et al (2003) and the results were recorded as positive or negative. The other variables studied were: sex; age in years, categorized as under 15 or 15 years-old and over; means of detection, contact examination, self-presentation or others; number of skin lesions, five lesions or less or six and above; number of thickened nerves, zero, one or more than one; disability grade at diagnosis, zero, 1 or 2 or not evaluated; bacilloscopy, positive, negative, or not tested; and bacilloscopic index, BI from zero to 6+ and categorized as negative, positive less than 2, positive two or higher, or not tested. The variable of disability
grade was used according to WHO criteria, as recommended by the Ministry of Health\textsuperscript{2,45}.

Final classification was defined as that used by the health center to determine patient treatment with MDT, taking into consideration the number of skin lesions and affected nerves in combination with bacilloscopy and ML Flow results. All patients with a positive BI were classified as MB, regardless of the number of skin lesions and thickened nerves.

The bacilloscopy was conducted on skin smears taken from four sites (skin lesion, both earlobes and the elbow on the other side of the body relative to the lesion; or in the absence of skin lesions, in both elbows). The slides were stained according to the Ziehl-Neelsen method, and the smears examined with an oil immersion lens (100x). The BI was calculated according to Ridley’s logarithmic scale from 0 to \(29\).\textsuperscript{2,45}

The association between ML Flow positivity and the variables under study was defined using odds ratio (OR) and a 95% confidence interval (95% CI), and univariate/multivariate analyses. For the multivariate analysis, the logistic regression method was used with the Hosmer & Lemeshow test to verify model adjustment\textsuperscript{11}. All variables were included that had a significance probability lower than 0.25 in the univariate analysis.

RESULTS

A descriptive analysis of the variables studied is presented in Table 1. Seropositivity in the ML Flow test occurred in 50.7% of the study participants. No predominance in seropositivity occurred between the sexes. Age varied from two to 98 years-old, with an average of 42, and 6.9% under the age of 15. In relation to the means of detection, 8.1% were diagnosed by way of household contact examinations, 29.5% via self-presentation and 62.4% through other means, mostly referral from other health centers. In this study, 38.9% of patients were attended at eight municipal health centers, 45.8% at four regional referral centers and 15.3% at two state referral centers.

Of the total cases researched, 59% were classified and treated as MB, 60.4% had five or fewer skin lesions and 7% had grade 2 disabilities. Among the 1,041 patients for whom data were available on the number of nerves affected, 38.7% had more than one thickened nerve. Bacilloscopy results were negative in 73% of cases, 7.8% had a positive BI under 2 and 19.2% had a BI of 2 or higher.

Univariate analysis between ML Flow and the other covariables showed that seropositivity was higher among men (58.6%); patients over 15 years of age (97.6%); those who had six or more skin lesions (64.7%); more than one affected nerve (52.4%); grade 1 disability (51%); grade 2 disability (10.4%); positive bacilloscopy (50.9%); positive BI under 2 (13.2%) and BI of 2 or higher (37.7%), Table 2.

In the multivariate analysis, seropositivity was statistically associated with patients 15 years of age or older (OR: 2.6); six or more skin lesions (OR: 7.5); more than one thickened nerve (OR: 2.4); positive BI under 2 (OR: 5.3); while the patient with a positive BI of 2 or higher had roughly a 191-fold chance of a positive serology compared to those with a negative BI (Table 3).

The probability of seropositivity increased as the number of affected nerves or skin lesions in the patient increased, although the rise was higher when the number of skin lesions increased (Table 4).
Although the under-15 age group represented a small percentage of all seropositive cases (2.4%), nearly a fifth (5.8%) of the children studied (17.6%) were seropositive. This fact may suggest that the number of MB cases in this age group is greater than expected, thereby further indicating the importance of ML Flow in the classification of leprosy in children.

Regarding the mode of detection, observation showed that referrals were the predominant source, something that was true for all new cases in the State in 2003. Although there were more male patients who presented seropositivity in this study, when the statistical models were adjusted for the other variables (multivariate analysis), no statistically significant association was observed between the variables of sex and seropositivity (Tables 2 and 3).

In reference to age, leprosy is a disease that occurs in young adults and the middle-aged, with a higher number of cases registered in the age group from 20 to 50 years; a fact confirmed in this study in which the average age was 42 years-old (Table 1), thus showing that leprosy affects the individual in the most productive years. The percentage of children under 15 years-old among the cases studied (6.9%) was higher than the average of all new cases diagnosed in Minas Gerais in 2003 (5.8%) yet lower than Brazil as a whole in that year (8%) (Table 1). Although the under-15 age group represented a small percentage of all seropositive cases (2.4%), nearly a fifth of the children studied (17.6%) were seropositive. This fact may suggest that the number of MB cases in this age group is greater than expected, thereby further indicating the importance of ML Flow in the classification of leprosy in children.

Regarding the mode of detection, observation showed that referrals were the predominant source, something that was true for all new cases in the State in 2003. This may be related to leprosy control training provided to Family Health Program teams, which in many cases still do not have the skills to diagnose cases, but can refer suspected cases from their areas of coverage for disease control.
confirmation of diagnosis in centers with greater experience. This procedure alters the means of detection, in that cases that would otherwise be listed as having been diagnosed by means of contact examination or self-presentation would be notified as referrals after confirmation of diagnosis in other referral centers.

In this study, the vast majority of patients presented no neural thickening or only one affected nerve (Table 1); less involvement of peripheral nerves was observed in relation to cases studied in Africa

The majority of subjects studied (60.4%) presented five skin lesions or less (Table 1), a fact also observed in Brazil by Lyon et al.

The percentage of grade 2 disability among the new cases analyzed (7%) is considered average by Ministry of Health parameters

The positivity of bacilloscopic results in this study (27%), while similar to other studies in the literature, was lower than that observed by Lyon et al. (35.9%) and by Castorina-Silva (40%) in a referral center in Minas Gerais, yet much higher than that obtained in Nepal (11.6%).

The probability of seropositivity increased according to the number of affected nerves or skin lesions, although the increase was higher with skin lesions. A patient with up to five lesions and more than one thickened nerve had a four-fold higher chance of being seropositive than a patient with zero or one nerve affected. A patient with six or more skin lesions and up to one thickened nerve had nearly a 16-fold probability of being seropositive than a patient with up to five lesions and zero or one nerve involved. A patient with six or more skin lesions and more than one thickened nerve had nearly a 18-fold probability of being seropositive than a patient with up to five lesions and zero or one nerve involved.

Therefore, the increased chance of seropositivity was greater with a higher number of skin lesions than with a higher number of affected nerves, while no multiplier effect was observed that might be expected from an increase in both variables (Table 4). This fact is in agreement with the operational classification that uses the number of skin lesions, but no longer includes the number of thickened nerves.

Seropositivity was statistically associated with patients over the age of 15 years-old, more than five skin lesions, more than one affected nerve and positive bacilloscopy, suggesting that ML Flow could be used as a reliable means of correctly classifying leprosy patients, ensuring the quality of patient treatment and disease control.

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