

Risk factors for physical disability upon release from multidrug therapy in new cases of leprosy at a referral center in Brazil

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ABSTRACT

The present study sought to investigate the risk factors for physical disability upon release from multidrug therapy (MDT) in new cases of leprosy, registered at a referral center in Brazil. This is a longitudinal and retrospective study that evaluated 260 patients. Multivariate analyses, using both the ordinal logistic regression, as well as the classification and regression tree (CART) algorithm were performed to determine the factors associated with physical disability upon release from treatment. The prevalence of disability did not differ significantly between diagnosis and release from treatment. Number of affected nerves and sensory impairment upon diagnosis were risk factors for disability at the end of MDT. The analysis using the CART algorithm resulted in the development of a clinical score to predict the risk of disability upon release from MDT. The decision tree may have a direct applicability in clinical practice for professionals dealing with leprosy, as it allows them to identify patients with a higher risk of physical disability through the use of simple and widely available clinical tests. This study also shows that the disability grade upon admission is the main risk factor for disability upon release from MDT. This result draws attention to the importance of early diagnosis in disability prevention.

KEYWORDS: Complications. Leprosy. Risk factors.

INTRODUCTION

Leprosy is a chronic granulomatous infectious disease caused by the intracellular bacterium *Mycobacterium leprae*, which affects the skin and peripheral nerves^{1,2}. It is the main infectious cause of disability and peripheral neuropathy in the world, presenting a greater importance in developing countries, where it is endemic^{2,3}. Neuropathy is the most serious manifestation of the disease, as it can lead to impairments and disabilities. These are crucial elements that differentiate leprosy from other diseases given that it has great physical, psychological and social implications^{4,5}.

In 2016, 12,437 new cases of leprosy with grade 2 disabilities (G2D) were reported globally, corresponding to 1.7 per million people. Although it represents a 12% reduction in the number of new G2D cases, when compared to 14,284 cases detected in 2015, some countries detected more new G2D cases in 2016 than in 2015⁶. Except for the year 2016, the number of new G2D cases has remained constant over the past ten years, within the range of 13,000 to 14,000, indicating a stagnation in leprosy control⁷. Due to the magnitude of the problem, the World Health Organization (WHO) launched in 2016 a 5-year global leprosy strategy to reduce the burden of disease. The

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strategy set three main targets to be achieved at global level by 2020: reduction of new G2D cases in children to zero, a reduction in the rate of new G2D cases to less than 1 case per million people and zero countries with laws that allow discrimination against leprosy⁶.

To treat leprosy properly, it is necessary to have an in-depth knowledge of its epidemiology and the determining factors of disability^{5,8}. Stagnation in the control of leprosy, especially in the number of new cases with grade 2 disabilities, emphasizes the need for further research on preventive measures⁷. More evidence of risk factors for nerve function impairment is important to prioritize the follow-up of high-risk patients and to develop disability prevention strategies⁹. Various studies have identified factors associated with physical disability upon diagnosis, such as age, sex, classification, duration of disease, number of skin lesions, number of affected nerves and socioeconomic factors^{5,10}. Studies that analyze risk factors for disabilities upon release from treatment are less common, especially in Brazil. As the epidemiology of the disease varies greatly worldwide, a certain population may present specific risk factors for disabilities, in addition to factors that are common to all populations. The present study aims to identify and quantify the factors associated with the presence of physical disability upon release from MDT in new cases of leprosy at a referral center in Brazil.

MATERIAL AND METHODS

Design

This is a longitudinal and retrospective study performed at Eduardo de Menezes Hospital (HEM), which is a public referral center in dermatology located in Belo Horizonte, Minas Gerais, Brazil. Clinical and sociodemographic information was collected from medical records and leprosy notification forms.

Study subjects and sample size

All new untreated cases of leprosy admitted to HEM for treatment over the period of 2005–2010 were eligible for this study. Patients who for any reason did not complete MDT at the referral center were later excluded. In the observed period, 342 new cases were reported. After analyzing the medical records, 82 patients were excluded (45 were transferred, 35 discontinued treatment and two died). Therefore, 260 new cases were included in the study.

As it was a convenience sample, the sample size calculation was not performed before the study. Considering the sensory impairment as the main factor to describe the

grade of disability upon release from MDT, a sample of 260 patients has a 99% power to detect the associations found at a significance level of 5%.

Procedures

The study procedures were part of the medical care routine of HEM. Upon admission, all patients were submitted to dermatoneurological examination, performed by a dermatologist, to confirm the diagnosis. Nerve function assessment was repeated every three months and upon release from MDT in asymptomatic patients. Nerve function was assessed monthly in patients with symptoms of neuritis or leprosy reactions, or under treatment for these conditions. The neurological examination followed recommendations set forth by the Brazilian Ministry of Health¹¹.

Upon admission, skin smears were collected from all patients, in ear lobes, one skin lesion and one sample from the elbow. As recommended by the Brazilian Ministry of Health, patients received MDT according to their operational classification¹².

The follow-up period of the study varied from six to nine months for paucibacillary cases (PB) and from 12 to 18 months for the multibacillary cases (MB). MB patients treated with alternative regimens without rifampicin were followed-up for 24 to 36 months.

Variables

The explanatory variables in the analyses included: age, gender, origin, schooling, method of case detection, number of skin lesions, number of affected nerves, type of neural alteration, operational classification, Madrid classification, bacteriological index (BI), leprosy reactions, type of treatment and disability grade upon diagnosis. The response variable was the disability grade upon release from MDT. All the explanatory variables, with the exception of reactions, were assessed at the time of diagnosis. The occurrence of leprosy reactions was investigated during the entire follow-up period.

Nerves were considered to be affected in the presence of nerve enlargement and/or sensory impairment and/or motor impairment. Sensory impairment was defined as a lack of response to 0.2 g monofilament (blue) on the hands and to 2.0 g (purple) on the feet. These reference values were based on a Nepalese study that assessed the touch sensibility in healthy volunteers¹³. Motor impairment was defined as any reduction in strength identified in the voluntary muscle testing.

The Madrid Classification was used to determine the clinical forms. For the operational classification, the number of skin lesions and BI were used. Patients with up to five

lesions were classified as PB and patients with six lesions or more as MB. In addition, all cases with positive BI were classified as MB¹².

Type 1 or 2 reactions were diagnosed when in the presence of reactional skin lesions, accompanied or not by evidence of neuritis. Nerve function impairment, with or without pain or nerve tenderness, and without other reaction symptoms, was classified as isolated neuritis.

Regarding treatment, MDT/PB and MDT/MB were categorized as standard MDT regimens. Therapeutic schemes substituting at least one of the drugs were classified in the same category: alternative MDT regimens.

The maximum disability grade was assessed upon admission and release from MDT, as recommended by the Brazilian Ministry of Health¹². Grade 1 disability was defined as the inability to feel the 2 g monofilament on the hands and feet, or the lack of immediate blinking in the eye exam using dental floss. Grade 2 disability was defined as the presence of one or more of the following alterations: lagophthalmos, ectropion, trichiasis, corneal opacity, a central visual acuity of less than 0.1 or an inability to count fingers at six meters, trophic and/or traumatic lesions on hands or feet, claws, absorptions, wrist drop, foot drop and ankle contractures¹².

Statistical analyses

The marginal homogeneity test was used to compare the disability grade upon diagnosis and release from treatment. In the univariate analyses, Pearson's chi-squared test or Fisher's exact test were used to compare the categorical variables, while the Kruskal-Wallis test was used to analyze the numerical variables. Non-parametric tests were used due to the asymmetric character of the analyzed variables.

For the multivariate analysis, an ordinal logistic regression model was used¹⁴. The variables with a p-value below 0.20 in the univariate analysis were included in the multivariate model. In the final model, the significant variables remained within the 5% significance level. A multivariate analysis was also performed by means of a decision tree, using the Classification and Regression Tree (CART) algorithm¹⁵. In this analysis, an improvement of at least 0.01 was used as a stop criterion. SPSS 15.0 and STATA 10.0 were used for statistical analysis.

Ethical approval

The study was approved by the Research Ethics Committee of Eduardo de Menezes Hospital, where the study was conducted, and by the Research Ethics

Committee of Federal University of Minas Gerais, for the master degree dissertation of one of the authors.

RESULTS

A total of 260 patients were included in this study, 138 males (53.1%) and 122 females (46.9%), with an average age of 44 years upon diagnosis. One hundred and sixty three of the cases were multibacillary (62.7%) and the most common form of the disease was the borderline (54.6%). During the follow-up period, 29 patients (11.2%) presented a type 1 reaction, 48 (18.5%) with isolated neuritis and 41(15.8%) presented a type 2 reaction. Upon diagnosis, nerve enlargement was observed in 70 (26.9%) of the cases, sensory impairment in 100 (38.5%), and motor impairment in 52 (20.0%), with the mean number of affected nerves reaching 2.5.

Upon diagnosis, 56 patients (21.5%) presented grade 1 disability, while 42 (16.2%) presented grade 2. The prevalence of disability did not differ significantly between diagnosis and release from treatment (Table 1). Among the 260 patients, 255 had the disability grade evaluated upon release from MDT and, therefore, were included in the univariate and multivariate analyses.

Table 1 - Comparison between the disability grade upon diagnosis and release from multidrug treatment (MDT) in new cases of leprosy reported at Eduardo de Menezes Hospital, 2005-2010.

	N	%
Disability grade upon diagnosis (n=260)		
Grade 0	162	62.3
Grade 1	56	21.5
Grade 2	42	16.2
Disability grade upon release from MDT (n=255)		
Grade 0	168	65.9
Grade 1	41	16.1
Grade 2	46	18.0

Note: n= number of cases. MDT- multidrug treatment; Marginal homogeneity test p-value = 0.297

The results of the univariate analysis for sociodemographic variables are illustrated in Table 2. The disability grade upon release from MDT was associated with schooling and the method of case detection (p-values <0.05). According to the univariate analysis, with the exception of the type of treatment, all clinical and quantitative variables were associated with the disability grade upon release from MDT (Tables 3 and 4).

In the multivariate analysis, the presence of sensory impairment upon diagnosis and the number of affected

Table 2 - Univariate analysis of the association between sociodemographic variables and disability grade upon release from multidrug treatment (MDT) in new cases of leprosy reported at Eduardo de Menezes Hospital, 2005-2010.

	Grade 0	Grade 1	Grade 2	p-value
Sex (n=255)				
Female	84 (71.2%)	19 (16.1%)	15 (12.7%)	0.111*
Male	84 (61.3%)	22 (16.1%)	31 (22.6%)	
Origin (n=227)				
Rural	5 (55.6%)	2 (22.2%)	2 (22.2%)	0.679**
Urban	143 (65.6%)	36 (16.5%)	39 (17.9%)	
Schooling years (n=171)				
None	5 (27.8%)	7 (38.9%)	6 (33.3%)	<0.001**
1 to 3	23 (47.9%)	13 (27.1%)	12 (25.0%)	
4 to 7	46 (79.3%)	7 (12.1%)	5 (8.6%)	
8 to 11	33 (86.8%)	2 (5.3%)	3 (7.9%)	
12 or more	8 (88.9%)	0 (0.0%)	1 (11.1%)	
Method of case detection (n=251)				
Voluntary report	33 (76.7%)	7 (16.3%)	3 (7.0%)	0.020**
Referral	111 (61.3%)	28 (15.5%)	42 (23.2%)	
Contact	22 (81.5%)	4 (14.8%)	1 (3.7%)	

Note: * Chi-square test ** Fisher exact test; n = number of cases

Table 3 - Univariate analysis of the association between clinical variables and disability grade upon release from multidrug treatment (MDT) in new cases of leprosy reported at Eduardo de Menezes Hospital, 2005-2010.

	Grade 0	Grade 1	Grade 2	p-value
Skin lesion count (n=250)				
1	55 (90.2%)	3 (4.9%)	3 (4.9%)	<0.001*
2 to 5	34 (75.6%)	6 (13.3%)	5 (11.1%)	
≥ 6	78 (54.2%)	30 (20.8%)	36 (25.0%)	
Nerve enlargement (n=255)				
No	145 (78.0%)	25 (13.4%)	16 (8.6%)	<0.001*
Yes	23 (33.3%)	16 (23.2%)	30 (43.5%)	
Sensory impairment (n=255)				
No	142 (91.6%)	11 (7.1%)	2 (1.3%)	<0.001*
Yes	26 (26.0%)	30 (30.0%)	44 (44.0%)	
Motor impairment (n=255)				
No	160 (78.8%)	30 (14.8%)	13 (6.4%)	<0.000*
Yes	8 (15.4%)	11 (21.2%)	33 (63.5%)	
Madrid classification (n=255)				
Indeterminate	20 (100%)	0 (0.0%)	0 (0.0%)	<0.001**
Tuberculoid	38 (90.4%)	2 (4.8%)	2 (4.8%)	
Borderline	82 (58.6%)	29 (20.7%)	29 (20.7%)	
Lepromatous	28 (52.8%)	10 (18.9%)	15 (28.3%)	
Operational classification (n=255)				
Paucibacillary	79 (84.9%)	7 (7.5%)	7 (7.5%)	<0.001*
Multibacillary	89 (54.9%)	34 (21.0%)	39 (24.1%)	
Leprosy reactions (n=255)				
None	114 (86.4%)	9 (6.8%)	9 (6.8%)	<0.001**
Neuritis only	17 (35.4%)	11 (22.9%)	20 (41.7%)	
Type 1 and 2	2 (33.3%)	1 (16.7%)	3 (50.0%)	
Type 1	15 (53.6%)	10 (35.7%)	3 (10.7%)	
Type 2	20 (48.8%)	10 (24.4%)	11 (26.8%)	
Treatment (n=255)				
Standard MDT regimen	140 (66.4%)	36 (17.1%)	35 (16.6%)	0.332*
Alternative MDT regimen	28 (63.6%)	5 (11.4%)	11 (25.0%)	

Note: * Chi-square test ** Fisher exact test; n= number of cases

Table 4 - Univariate analysis of the association between age, number of affected nerves, bacteriological index and disability grade upon release from multidrug treatment (MDT) in 255 new cases of leprosy reported at Eduardo de Menezes Hospital, 2005-2010.

	Grade 0	Grade 1	Grade 2	p-value
Age				
Mean	41.5	50.9	50.3	<0.001*
Standard deviation	15.9	15.7	15.8	
Minimum	3.0	12.0	18.0	
Maximum	77.0	83.0	79.0	
25 th percentile	31.3	40.0	39.8	
Median	41.5	54.0	49.5	
75 th percentile	52.8	61.0	65.0	
Number of affected nerves				
Mean	0.6	3.8	8.9	<0.001*
Standard deviation	1.3	3.1	4.6	
Minimum	0.0	0.0	1.0	
Maximum	9.0	12.0	18.0	
25 th percentile	0.0	1.0	5.0	
Median	0.0	3.5	9.5	
75 th percentile	0.0	6.0	12.0	
Bacteriological index				
Mean	0.9	1.4	1.5	<0.001*
Standard deviation	1.7	1.7	1.7	
Minimum	0.0	0.0	0.0	
Maximum	6.0	5.0	5.0	
25 th percentile	0.0	0.0	0.0	
Median	0.0	0.0	0.5	
75 th percentile	0.8	3.0	3.0	

Note: * Kruskal-Wallis test

nerves were the main factors associated with the disability grade determined upon release from MDT (Table 5). The model presented a good adjustment, according to Deviance statistics.

Factors associated with the disability grade upon release from MDT, according to the CART algorithm were the number of affected nerves, presence of sensory impairment and gender (Figure 1). The number of affected nerves upon admission was the main factor associated with the disability grade upon release from treatment. Patients with three or more affected nerves presented a 54.7% probability of having grade 2 disabilities by the end of the treatment. In this patients' subgroup, it was also observed that when more than nine nerves were affected, this probability increased even further, reaching 95.7%. By contrast, patients with up to two nerves affected upon admission presented less

chances of disability. To assess the disability risk in this subgroup of patients, the second important factor was sensory impairment upon diagnosis. The presence of this type of impairment increased the probability of grade 2 disability from 1.3% to 11.1%. The male gender was the third factor associated with the presence of disability upon release from treatment in a small subgroup (patients with up to two affected nerves and with sensory impairment). The model presented good adjustment with an estimated risk of 0.19 indicating that the decision tree is able to correctly classify 81% of data variability.

The decision tree presented above did not take into consideration the disability grade upon admission. When the initial disability grade was added to the multivariate analysis, only this variable remained in the final model. The decision tree that includes this variable shows the

Table 5 - Factors associated with the disability grade upon release from multidrug treatment (MDT) in the multivariate model, in new cases of leprosy reported at Eduardo de Menezes Hospital, 2005-2010.

Variables	p-value	Grade 0 x Grade 1		Grade 0 x Grade 2	
		OR	CI 95%	OR	CI 95%
Sensory impairment	<0.001	6.80	[2.68 - 17.24]	45.36	[7.11 - 289.20]
Number of affected nerves	0.031	1.35	[1.08 - 1.68]	1.81	[1.17 - 2.81]

Note: Deviance = 120.75 (p-value = 0.999)OR: odds ratio CI: confidence interval

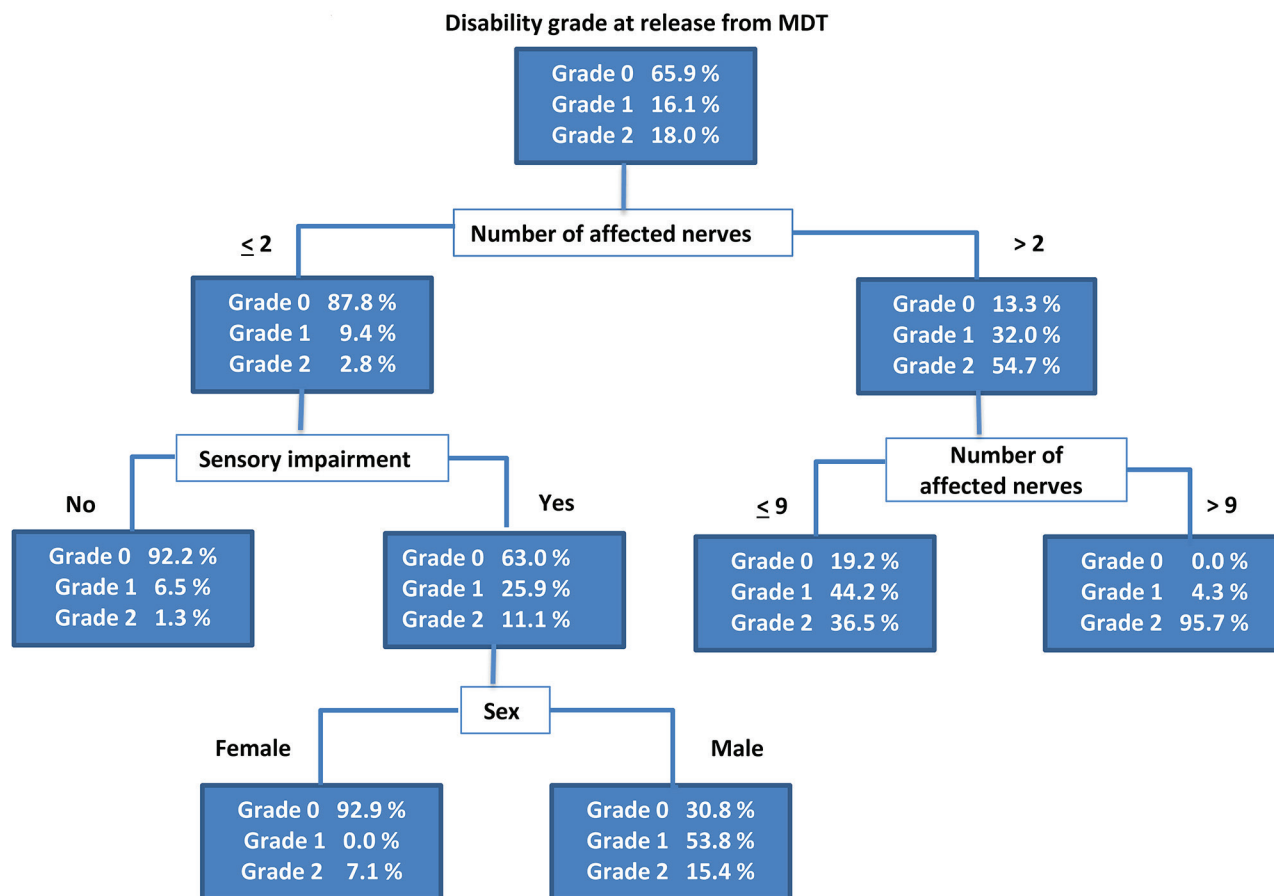


Figure 1 - Classification and regression tree for factors associated with the disability grade upon release from multidrug therapy (MDT) in new cases of leprosy.

progression of the disability grade from diagnosis to the end of treatment (Figure 2). Patients with grade 1 disability upon admission presented a 10.7% probability of evolving to grade 2 upon release from MDT, whereas patients already admitted with grade 2 disabilities have a 95.2% probability of remaining the same by the end of treatment. No patients admitted with grade 0 evolved to grade 2 upon release from MDT.

DISCUSSION

The factors associated with physical disabilities upon release from MDT were the number of affected nerves, sensory impairment, and, primarily, the presence of physical disability upon diagnosis. A multivariate analysis using ordinal logistic regression showed that the risk of physical disability upon release from MDT progressively increases with an increasing number of affected nerves upon admission. For each affected nerve presented upon admission, the chance of presenting grade 1 disability at the end of treatment increased by 1.35 fold, while the risk of having grade 2 disability increased by 1.81 fold. Ordinal

logistic regression also showed that the presence of sensory impairment upon diagnosis increased by almost seven times the chance of presenting grade 1 disability and by 45 times the chance of presenting grade 2 disability upon release from MDT.

The multivariate analysis, using the CART algorithm, showed similar risk factors and supported the findings from ordinal logistic regression. It also enabled the development of a decision rule that may have direct applicability in the clinical practice of professionals dealing with leprosy. The decision tree allows for these professionals to identify patients with an increased risk of physical disabilities, and who should thus be followed up more carefully. Another advantage of the decision tree is that the factors used to predict the risk of disability upon release from MDT can be assessed with simple and widely available clinical tests (nerve palpation, sensory testing and voluntary muscle testing). Although promising, the applicability of the clinical rule needs to be confirmed by additional research, including prospective studies in different populations.

However, when the disability grade upon diagnosis was included in the multivariate analysis, only this variable

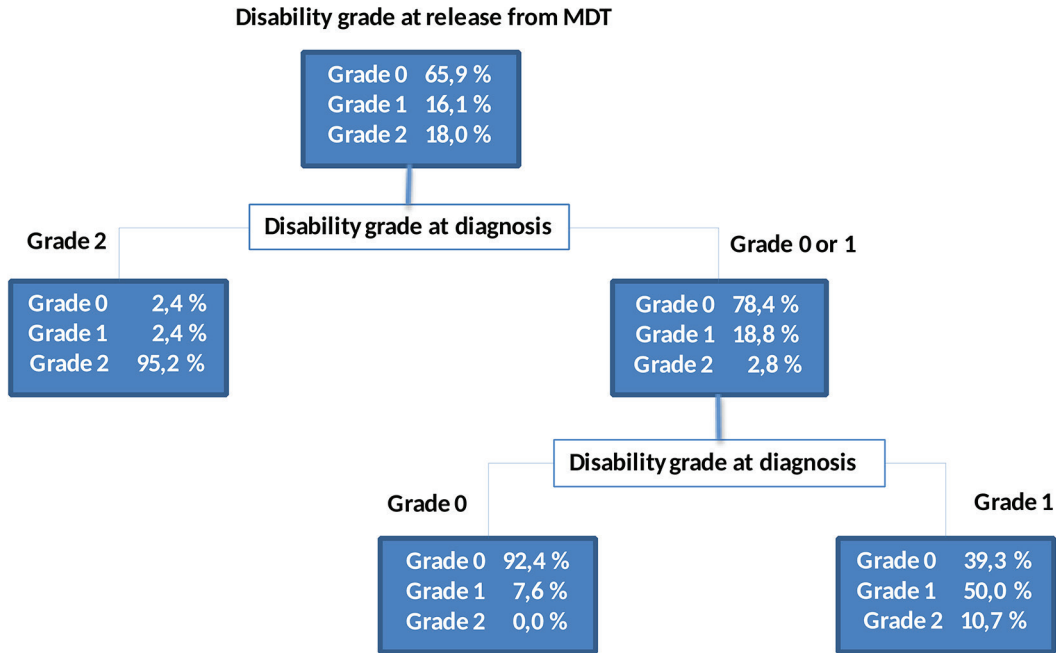


Figure 2 - Classification and regression tree that shows the progression of the disability grade from diagnosis to the release from treatment in new cases of leprosy.

remained in the final model, which indicates that the disability grade upon admission is the main risk factor for disability upon release from MDT.

The main limitation of the study is the fact that it is retrospective, with the possibility of information bias. The development of the present study in a referral hospital in Brazil, with high rates of multibacillary cases and impairment upon diagnosis, limits the extrapolation of results to other contexts, such as basic health units and other populations.

A broad variation was observed in the prevalence of nerve function impairment and physical disabilities due to leprosy in different studies. One cohort study in Bangladesh showed sensory impairment in 11.9% of the cases and motor impairment in 7.39%¹⁶, while, in a study conducted in Nepal, sensory and motor impairment occurred in 29.0 and 24.0% of cases, respectively¹⁷. In the present study, the prevalence of nerve function impairment was high. Sensory impairment was observed in 38.5% of the cases and motor impairment in 20.0%. In relation to the disability grade upon diagnosis, the percentage of patients with grade 1 and grade 2 was, respectively, 9.6% and 5.9% in Bangladesh¹⁶, 11.0% and 7.3% in Thailand¹⁸, 29.1% and 10.1% in Minas Gerais¹⁰, and 31.0% and 27.0% in Ethiopia¹⁹. The present study also showed high rates of disability upon diagnosis (21.5% of grade 1 and 16.2% of grade 2), even though these rates were still lower than those reported in Ethiopia. Differences in the prevalence of nerve function impairment and physical disability could be explained by several factors,

including differences in patient selection criteria, in the proportion of MB cases in the population, in the disability grading system used, and in the nerve function assessment. Studies that assess tactile sensations using a ballpoint pen, as is the case of cohorts in Bangladesh and Thailand, could underestimate the prevalence of sensory impairment^{16,18}.

The proportion of new cases with grade 2 disability upon diagnosis among all new cases detected during the year is used as an indicator of the quality of case detection activities. Percentages equal to or greater than 10% are considered high¹². In Brazil, there was an increase in the proportion of new cases detected with grade 2 disabilities from 7.5% in 2015 to 8,3% in 2017²⁰. The high prevalence of grade 2 disability upon admission in the present study (16.2%) could be related to the fact that it was conducted in a referral center which deals with high complexity cases, as well as to the delay in diagnosis, due to the lack of awareness of the early warning signs of disease and the low capacity of basic health care units to recognize and treat leprosy as early as possible.

The multivariate analysis findings support previous studies showing that the number of affected nerves and the presence of nerve function impairment upon diagnosis were associated with physical disabilities. In a Nepalese study, the presence of more than three enlarged nerves increased the chance of impairment by 3.3 fold¹⁷, while a cohort study in India showed that the presence of more than four enlarged nerves increased the risk of impairment by 1.2 fold⁹. A retrospective study in Belo Horizonte, Minas

Gerai State, Brazil, showed that the chance of disability was 10 times higher for patients with three or more affected nerves²¹, a cohort in India showed that the presence of palmo-plantar anesthesia upon diagnosis increased the chance of disability at the end of treatment by 2.4 fold²². In a study from Bangladesh, risk factors for nerve function impairment during two years of follow-up included MB classification, the presence of one or more enlarged nerves, and primarily, nerve function impairment upon diagnosis (hazard ratio of 7.4)²³.

Few studies in the literature have used CART algorithms to analyze risk factors for disability in leprosy. In a retrospective study conducted in a basic health care unit in Belo Horizonte, Minas Gerais State, Brazil, the factors associated with progression in the disability grade, in a multivariate analysis using the decision tree included: disability grade upon admission, type of physiotherapy treatment, dose of steroids, age, number of affected nerves and occurrence of leprosy reactions²¹.

The present study showed that the disability grade upon admission is the main risk factor for disability upon release from MDT. Other studies have similar findings. A retrospective study in Bangladesh showed that only 1.6% of the PB and 7.9% of the MB patients without initial disabilities presented nerve function impairment during the period of treatment²⁴. A cohort study conducted in Ethiopia, with 592 new leprosy cases, compared the maximum grade of disability and the eye-hand-foot impairment score (EHF score) at three moments: admission, release from treatment and between 24 and 48 months after release from MDT. Overall, the EHF score distributions did not change significantly over time²⁵. The Ethiopian cohort study demonstrated that the initial disability grade is still the main prognostic factor even five years after release from treatment. Patients with initial EHF scores of 1 or 2 had a relative risk of 9.1, whereas patients with scores equal to or higher than 3 presented 65 times higher risk of disability five years after release from MDT²⁶.

CONCLUSION

The findings of the present study corroborate those of previous studies developed in different countries, demonstrating that risk factors for disabilities in Brazil are similar to the ones found in other populations. Thus, strategies to reduce the prevalence of disabilities could be developed globally, with contributions from all highly endemic countries.

The present study reinforces that the greater the disability grade upon admission, the higher the probability

of disability upon release from MDT. It is known that the presence of disability upon admission is an important indicator of delay in diagnosis. Therefore, this study emphasizes the great importance of early detection and treatment of leprosy to prevent disabilities and deformities.

The major impact of this study in the clinical practice is the development of a clinical score that can be used to predict the risk of disability at the end of treatment. The decision tree is based on simple clinical tests, which are available worldwide with no additional costs and can be applied in a wide range of health services. It may be useful in other settings, but it must be externally validated before its application can be scientifically justified in other populations. Nonetheless, we expect that patients in other settings will behave similarly since the risk factors for physical disabilities are similar, as are the almost universal methods of nerve-function assessment and treatment in leprosy. Additional research, including prospective studies in different populations, is required to confirm the applicability of the decision tree in daily practice.

AUTHORS' CONTRIBUTIONS

Barbara Proença Nardi Assis was responsible for the data collection, contributed to the study planning, analysis and interpretation of the results and drafted the manuscript. Sandra Lyon contributed to the study planning, analysis and interpretation of the results. Maria Aparecida de Faria Grossi contributed to the analysis and interpretation of the results. Manoel Otávio da Costa Rocha contributed to the study planning, analysis and interpretation of the results. All authors revised the manuscript for intellectual content and approved the final version.

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