

Temporal Analysis of a Case Series of Leprosy Patients From a Low Endemic Area in Brazil and the Magnitude of Disability

ORIGINAL

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Abstract

Leprosy is an infectious disease caused by *Mycobacterium leprae* infection. The incubation period after the primary infection can be as long as decades. This bacterium has a tropism for macrophages and Schwann cells and as result neuropathies are frequent. The state of Rio Grande do Norte in northeastern Brazil has areas of low and high endemicity for leprosy. The aim of this study was to analyze a leprosy time series from Rio Grande do Norte, from 2005 to 2014, based on data provided by the Notifiable Diseases Information System from the State Secretariat of Health. This was a quantitative, descriptive and analytical study. We considered variables such as sex, age, clinical form, operational classification and disability grade at diagnosis. There were 3,426 cases of leprosy reported of which 1,781 were females (52%). Of those patients, 29% presented disability at diagnosis. The high level of disability in patients along with the lack of information regarding disability levels indicates the need for more effective measures, with early diagnosis to decrease morbidity as leprosy still remains as a serious public health problem.

Introduction

Leprosy is an infectious disease caused by *Mycobacterium leprae* infection [1]. This bacterium presents a slow growth but leads to disease development that can be accompanied by the development of severe disability [2]. *M. leprae* has a particular tropism for Schwann cells,

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with frequent neuropathy, which is a main cause of disability. The neuropathies are usually mixed, with damage to sensory, motor and autonomic nerve fibers, resulting in deformities and permanent disability [3, 4].

It is essential to conduct neurological assessment throughout treatment, which is usually recommended at the beginning, during, and at the end of treatment, or based on whenever clinical signs or symptoms of neuritis develop [5]. The course of the disease can be measured through the assessment of the level of disability in the patient. Clinical manifestations of the neuritis can be estimated by the severity of the pain, nerve hypersensitivity, edema, sensory and motor functions. However, the neuritis may evolve with no pain, which is termed silent neuritis, which can be identified during the neurological assessment [3, 6, 7].

Although there is effective free available treatment for leprosy, it still remains a major public health issue in many areas of the world, including Brazil, which is the country with the second highest number of new cases detected each year [8, 9]. Understanding the epidemiology and identifying clustering of disease is essential to develop intervention measures.

In Brazil's northeast region leprosy has persisted with a high number of cases over the years, but some of northeastern states have a level of endemicity considered within the standards of elimination, such as the State of Rio Grande do Norte (RN) [10]. This state showed a significant reduction in the prevalence of leprosy with a current rate of 0.74 cases/10,000 inhabitants. However, within the state, there are areas of high endemicity with new case detection greater than 40 per 100,000 [11-13].

Thus, the state of Rio Grande do Norte has been heterogeneous in the level of leprosy case detection over the years. While there are municipalities that do report cases, others are considered hyper-endemic and thus have been targeted as locations of high priority by the Brazilian Ministry of Health [14]. In general, leprosy is a silent disease that re-

quires effective participation of health staff at the community level to allow for early diagnosis and prompt administration of treatment.

Rio Grande do Norte, similar to many other Brazilian states, has referral centers for leprosy diagnosis. Of concern, has been the increase in case detection in children under 15 years of age, with grade II disability at diagnosis, indicating a very late identification. The aim of this study was to analyze a time series of leprosy cases in Rio Grande do Norte, northeastern Brazil, between 2005-2014, based on data provided by the Notifiable Diseases Information System, from the State Secretariat of Health.

Methods

Study area

The State of Rio Grande do Norte is located in Northeast Brazil and has 167 municipalities, with an estimated population in 2015 of 3,442,175 inhabitants living in an area of 52,811.126 km². Its population density is 59.99 inhabitants/km² with per capita monthly income of \$248.00. The state capital is Natal, located on the state's eastern coast [15].

Source of data

This is a descriptive and analytical study, which was based on cases of leprosy from the State of Rio Grande do Norte, reported to the Minister of Health between August 2005 to October 2014.

Statistical Analysis

Graphical analyzes and calculations of prevalence as well as analysis of differences in sex, age, clinical form, operational classification, and degree of disability were completed using Excel (Microsoft, Redmond, WA), R version 3.3.1 "Bug in Your Hair" statistical software with epiR package, and Graph Pad Prism version 6.05 (Graph Pad Software Inc., La Jolla, CA). Pearson chi-squared test was used to compare clinical forms of diseases in males and

females. One-way ANOVA with Tukey's multiple comparisons test was utilized to assess differences in the types of clinical forms and degree of disability within the study.

Ethical considerations

The protocol was assessed and approved by the Universidade Federal do Rio Grande do Norte Ethical Committee (CEP-UFRN) and by the Brazilian National Ethical Committee (CONEP/CNS/Ministério da Saúde, Brasília). All participants or their legal guardians signed informed consent forms prior to sample collection.

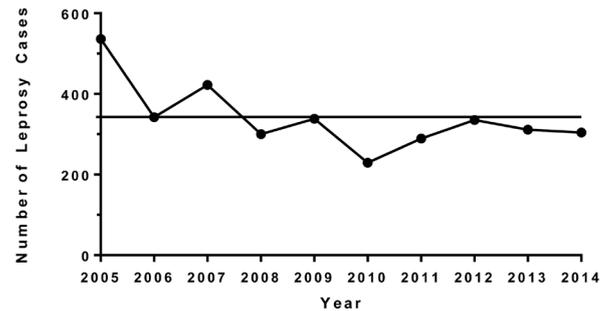
Results

A total of 3,426 cases of leprosy were diagnosed in the state of Rio Grande do Norte between 2005 and 2014 (**Figure 1**). There were slight variations from the average number of leprosy cases identified each year in 2005, 2007, and 2010 but the remaining years were more homogeneous in detection rates, as shown in **Figure 1**.

Of the 3,426 cases, 1,781 were females (52%) (**Figure 2**), with no significant difference between the number of males and females with leprosy throughout the study (p-value=0.5051 (CI:-28.41, 55.61). When controlling for sex, there was a statistically significant difference in the number of cases of leprosy based on age. There were more cases of leprosy among individuals 15 years of age or older compared to 0-14 years of age in both males and females. (males p-values: <0.0001) (females p-values: <0.0001).

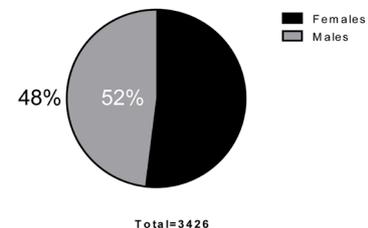
When analyzing clinical forms of disease it was found that females were twice as likely as males to present with indeterminate or tuberculoid forms of disease (OR:2.03, p-value=<0.0001 and OR:2.14 p-value=<0.0001, respectively) (**Table 1 & Figure 3**). Males were more likely to present with Dimorphous or Lepromatous forms of disease (OR: 1.56 p-value=<0.0001 and OR: 2.89 p-value=<0.0001,

Figure 1: Leprosy cases reported for the State of Rio Grande do Norte, Brazil from 2005 to 2014. Natal/RN. Straight line represents average number of leprosy cases across time series (342.6). Total number of cases across all 10 years was 3,426.



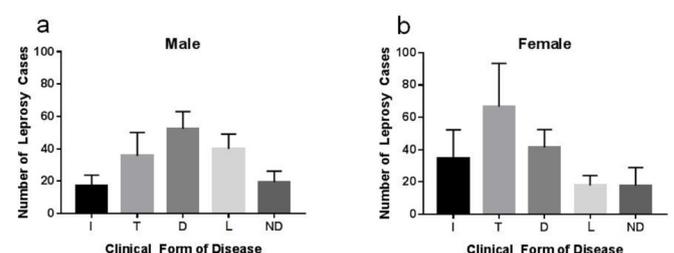
Data source: Information System for notifiable Diseases.

Figure 2: Cases of Leprosy reported in the State of Rio Grande do Norte, Brazil from 2005 to 2014. Natal/RN based on sex.



Data source: Information System for notifiable Diseases.

Figure 3: Distribution of Clinical Forms of Leprosy Based on Sex in the State of Rio Grande do Norte from 2005-2014. I=Indeterminate, T: Tuberculoid, D: Dimorphous, L: Lepromatous, ND: Not Determined. a) is the distribution of clinical forms of leprosy in males; b) is the distribution of clinical forms in females.



Data source: Information System for notifiable Diseases.

Table 1. Distribution of clinical forms of Leprosy based on sex.

Clinical Form	Male		Female		Total	P-Value
	N	%	N	%		
Indeterminate	172	33.3	344	66.7	516	<0.0001
Tuberculoid	357	34.9	667	65.1	1024	<0.0001
Dimorphous	524	55.9	413	44.1	937	<0.0001
Lepromatous	400	69.1	179	30.9	579	<0.0001
Not Determined	192	51.9	178	49.4	360	0.1272
Total	1645		1781		3426	

Table 2. Distribution operational classification of leprosy cases based on sex.

Operational Classification	Male		Female		Total	%
	N	%	N	%		
Multibacillary	1074	65.3	695	39.0	1769	51.6
Paucibacillary	569	34.6	1082	60.8	1651	48.2
Not Documented	2	0.1	4	0.2	6	0.2
Total	1645		1781		3426	

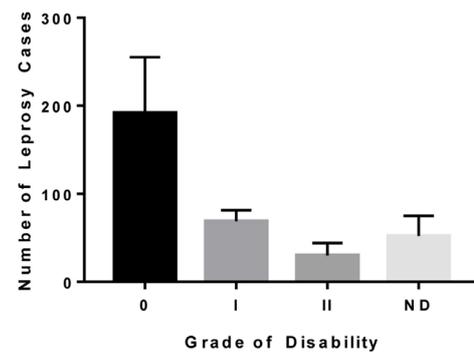
respectively). Furthermore, when controlling for sex it was seen that the dimorphous form of disease was more common than any other form of disease within males and Tuberculoid form within females. While it was not statistically significant there were slightly higher odds of not having a clinical form reported for male patients compared to female patients (OR: 1.19 p-value=0.1272).

Additionally we found that, 51.7% of the cases were Multibacillary and of these 60.7% were males, as shown in **Table 2**. When analyzed the mean number of multibacillary cases among males was higher than the mean number of paucibacillary cases (p-value=<0.001). Furthermore, in females there was a higher number of paucibacillary cases versus multibacillary (p-value 0.0096).

The degree of disability measured at the time of diagnosis, of the 3,426 cases, was as follows: 1,916 (59.6%) had grade 0 of disability, 689 (20.1%) presenting with grade I, 301 (8.1%) presenting with

grade II, and 520 (15.1%) did not have available data on disability level (**Figure 4**). Statistical analysis showed that grade 0 was more common than grades I and II (p-value= <0.0001 and <0.0001, respectively). Furthermore, while the difference was statistically significant grade I was slightly more common than grade II (p-value 0.0811).

Figure 4: Distribution of Disability Grades of Leprosy in the State of Rio Grande do Norte from 2005-2014. 0=Grade 0, I=Grade 1, II=Grade 2, ND=Not Determined.



Data source: Information System for notifiable Diseases.

Discussion

Brazil is the country with the second highest number of new cases reported for leprosy [16,17]. The disease is clustered within low and high endemic areas. The state of Rio Grande do Norte is considered a low endemic area [10], however, as previously reported [10, 13], there are municipalities with high rates of case detection. In our study, we observed variations in the number of cases reported, which might be associated with active case searches, such as those in Mossoró [11-13].

In the state of Rio Grande do Norte, children under 15 corresponding to 15% of all cases. Leprosy affects people of all ages [18]. Leprosy in children is usually reported in areas with greater endemicity of the disease [8]. In 2011, the Brazilian Ministry of Health recorded 33,955 new cases of leprosy,

of which 2,420 (7.12%) were diagnosed in children under 15 years of age. In the state of Pará, in the Amazonas region, in 2011, the overall rate of new cases in children under 15 years was 18.29/100,000 inhabitants. In Brazil, an annual detection rate above 10/100,000 is considered hyperendemic [19]. Therefore, our observations and those from other parts of Brazil signal to the need to deliver active search within the areas of high endemicity to diagnosis cases at earlier stages.

The distribution by sex observed in this study is similar to other places in Brazil, with disease affecting both sexes, but women tend to present as paucibacillary, with indeterminate or tuberculoid forms [20]. Multibacillary cases are the source of infection and maintenance of the endemicity. However, after a few weeks of antibiotic therapy there is a significant decrease in transmission, because the first doses of medication inactivate bacilli and make them unable to infect others [21, 22].

A study in Brazil's southeastern region of cities found that professionals in primary health care had little knowledge about the disease, which hampered the organization of municipal programs for the control and prevention of disease. This lack of knowledge resulted in inadequate approaches and impresses the need for training

Regarding the indicator "assessment of the degree of disability", which should be analyzed at diagnosis, we found that there was a lack of initial assessment in 15% of leprosy cases. This fact arouses some concern since it could result in more physical disability. Neurological assessment defines the degree of disability due to the risk of the development of irreversible neurological damage. The particular tropism that *M. leprae* has for the nerve fibers is a detrimental factor that can lead to neuropathy. When the peripheral nerves are affected by bacilli, there is a loss of thermal and tactile sensitivity, and deep painful sensitivity. The response to inflammation can be varied from minor responses in functional changes to the granulomatous infiltra-

tion of the entire neural parenchyma that can lead to the destruction of peripheral nerves and loss of function [2, 4]. Therefore, these results emphasize the need for neurological assessment of all patients affected by leprosy.

Often the neuritis is accompanied by intense pain, nerve hypersensitivity, edema, sensory and motor function. However, these phenomena can develop without pain as in the case of silent neuritis [3, 23]. When there is no pain or nerve hypersensitivity, the possibility of changes in sensitivity is a signal to aware. In order to monitor the evolution of complications, it is recommended frequent neural assessment, serious nerve damage can occur and can severely compromise the activities of daily life for patients [2]. Thus, this assessment at the beginning of treatment sets allows for the assessment of sensitivity changes, which are an alarming sign of nerve damage, even if the person does not present any complaints [2, 4]. The main action plan for the Ministry of Health, to achieve low endemic levels of leprosy, is based on the organization of a network with integration of control strategies and early detection of new cases. Emphasis on treatment with multidrug therapy, prevention of disabilities and surveillance of household contacts are encouraged [24; 5]. The system also includes the monitoring of patients in primary health care settings, according to each region or district health system, and maintenance/specialization of care in specialized networks in the secondary and tertiary levels when necessary [26].

Conclusions

The data demonstrate the need for the development of many actions in order to control leprosy. It is important to note the heterogeneous distribution of the disease in the municipalities of this northeastern Brazilian state, because it is a silent disease in its early stages. This feature reinforces that activities should be carried out in accordance to the region

endemicity, since the incidence of leprosy varies greatly within the Brazilian regions. Thus, the work needs to be intensified in priority municipalities. This study contributes to a better understanding of endemic disease, in order to direct the actions in state such as RN, which could be a model for intervention. It is true that health education carried out through educational campaigns should be a constant activity, in addition to professional training. The high turnover of health professionals is also a consistent problem and therefore the authorities should always be vigilant and prepared for this phenomenon, with effective plans to overcome this obstacle.

It is possible to conclude the state still cannot control leprosy and needs more effective strategies for combating the disease. The healthcare professional must be alert, and intensify surveillance around areas that have reported leprosy. It should be emphasized that it is essential to have the support of all professionals, managers, and people affected by leprosy, in order to gain full control of this disease.

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