Multibacillary leprosy and the elderly: a field for further research

MAURICIO LISBOA NOBRE*,**,***, FRANCIANNE MEDEIROS AMORIM**, MÁRCIA CÉLIA FREITAS DE SOUZA****, FERNANDA SALOUM DE NEVES-MANTA*****,
DANUZA ESQUENAZI******, MILTON OZORIO MORAES*****,
EUZENIR NUNES SARNO***** &
SELMA MARIA BEZERRA JERONIMO********

*Hospital Giselda Trigueiro, Natal/RN, Brazil
**Instituto de Medicina Tropical do Rio Grande do Norte, Universidade Federal do Rio Grande do Norte, Natal/RN, Brazil
***Post-graduate Program in Tropical Medicine, Instituto Oswaldo Cruz, Fiocruz, Rio de Janeiro/RJ, Brazil
****Instituto Nacional de Seguridade Social (INSS), Mossoró/RN, Brazil
*****Laboratório de Hanseníase, Fundação Oswaldo Cruz, Rio de Janeiro/RJ, Brazil
******Instituto Nacional de Ciência e Tecnologia de Doenças Tropicais (INCT-DT), Salvador/BA, Brazil

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Summary

Introduction: Leprosy is an important public health problem in Brazil where 28,761 new cases were diagnosed in 2015 and 7.3% were among children, indicating active transmission.

Objectives: This study was designed to analyse leprosy indicators in a Brazilian municipality (Mossoró, RN) and to identify the burden of Mycobacterium leprae infection among elderly residents using ML-Flow assay.

Results: Leprosy continues to be hyperendemic in Mossoró and does not present signs of decline. However, both the general new case detection rate and the detection of MB cases were higher among 60–79 year olds. The percentage of new cases classified as MB increased progressively by age group and reached 67.7% among...
those with 60 or more years of age (180/266). A hyperendemic neighbourhood was
selected for a diagnostic campaign and a total of 504 elderly individuals were tested
with ML Flow test, which was strongly positive in four people (0.8%) and samples
from skin biopsy of these subjects were also qPCR positive. Two new MB cases were
confirmed, one of which had no cutaneous lesions.

Conclusions: MB leprosy appears to be more frequent among the elderly regardless
of whether the disease is experiencing or not a period of decline. According to our
results and literature review we hypothesized that the greatest incidence of leprosy
by age apparently is related to the life expectancy of the population. These
characteristics suggest that active case finding campaigns for untreated MB leprosy
among the elderly may be useful in endemic areas as an innovative complementary
strategy to interrupt the transmission of \textit{M. leprae}. 

Introduction

Leprosy continues to be an important public health problem in the world since multidrug
therapy (MDT) did not result in the expected decrease of newly detected cases annually.
Some authors believe we are living in a troublesome time for disease control globally and the
fight against leprosy seems to have stalled, making necessary the adoption of new strategies
to effectively reduce the transmission of \textit{Mycobacterium leprae}.\textsuperscript{1,2}

Brazil reported 28,761 new cases of leprosy in 2015, of which 2,113 were diagnosed
among children under 15 years (7.3%) and 1,880 were detected with disability Grade 2 (7.5%
of assessed patients).\textsuperscript{3} These data show that leprosy continues to be an important public health
problem with active transmission in the country and remains an important cause of permanent
disability.

Leprosy is hyperendemic in the municipality of Mossoró, located in the State of \textit{Rio Grande
do Norte} (RN), in northeastern Brazil. From 2001 to 2013 the municipality presented a mean
new case detection rate (NCDR) of 45.4 new cases per 100,000 residents\textsuperscript{4} and, despite constant
diagnostic campaigns, good surveillance of leprosy household contacts and high coverage of
MDT over several years, the NCDR has not shown signs of decreasing over the years.

The main source of infection with \textit{M. leprae} is believed to be contact with patients with
multibacillary (MB) leprosy; therefore, it would seem logical that the strategies for
interrupting transmission would include activities aimed at detecting and treating individuals
with this form of leprosy. However, diagnostic campaigns generally search for skin lesions
with sensory loss which sometimes is not present in MB cases.\textsuperscript{5}

The objective of this study was to analyse the leprosy indicators in the municipality of
Mossoró, RN, with special attention to MB leprosy. In an attempt to reduce the source of
infection by \textit{M. leprae} in the community, the NCDR of this form of disease was calculated by
age group and by municipal surroundings aiming to identify target populations and areas for
the development of new strategies for MB case detection.

Material and Methods

Data Collection

The number of cases notified in the municipality from 2001–2013 was obtained from the
State Health Department (SES-RN) database, called SINAN (from Portuguese National
Notifiable Diseases Information System). Data regarding the overall population of Mossoró
(2001–2013) by neighbourhood, age and sex were obtained from IBGE (from Portuguese, the Brazilian Institute of Geography and Statistics).

Epidemiological indicators

The main indicators utilised for leprosy monitoring were calculated. SINAN data were analysed using Epi Info (Version 7.0.9.7), generating data tables grouped by year of diagnosis, neighbourhood of residence, sex, age group and operational classification. The tables were exported to Microsoft Excel (Version 14.0.4760.1.000) where indicators were calculated. The mean NCDR (2001–2013) was obtained by dividing the average annual number of new cases (by neighbourhood of residence and age group) by the population in 2007. The results are expressed per 100,000 inhabitants.

Study population

Mossoró had an estimated population of 291,937 residents in 2016. The Census of 2010 identified that 91.3% of the population was urban, 23.5% of the residents were under 15 years old, and 9.3% were 60 years old or older. From 2001–2013 the neighbourhood of Belo Horizonte and residents from 60–79 years presented the highest mean NCDR of MB leprosy of the municipality, explaining the selection of these groups for active case-finding in 2016. In the parts of the neighbourhood covered by the Family Health Strategy the estimated population is 6,052, of which 665 are 60 years old or older and were the target population of this study.

Procedures

1. Serology: Considering that a very high percentage of patients with MB leprosy present positive anti-PGL-1 serology, the ML Flow test (produced by the Federal University of Goiás, Brazil) was utilised for the selection of seropositive patients for medical evaluation. The results were analysed according to the previously published protocol and classified as negative or positive (1+, 2+, 3+ or 4+). 8
2. Home visits: a team consisting of 12 nursing students and seven community health workers visited all of the households in the study area. The study objectives were explained to the individuals 60 years old or older through a term of free and informed consent and the volunteers conducted the serological test.
3. Evaluation at the health clinic: All seropositive residents underwent a total body dermatological examination and a simplified neurological evaluation. Consultations were conducted by two physicians, specialists in leprosy.
4. Bacillary loads: All residents with strongly positive serology (3+ or 4+) underwent slit skin smears of both earlobes and elbows according to the nationally utilised protocol. 9
5. Skin biopsy: Given that one of the participants with strongly positive serology also had a positive skin smear, despite the fact that he had no visible skin lesions, a skin biopsy was taken to assess possible cutaneous infiltration in this patient and two other similar cases (strongly positive serology without clinical signs of leprosy).
6. Polymerase chain reaction (PCR): Skin biopsy specimen and nasal mucosal swabs were used to investigate the presence of *M. leprae* DNA by PCR. DNA extraction was performed according to previously published protocols. 10,11 The 85B DNA and 16S rDNA were targeted by the StepOne Real-Time System (Life Technologies).
ETHICAL CONSIDERATIONS

This study was previously approved by the Ethical Research Committee of the Federal University of Rio Grande do Norte (CAA 06189612.9.0000.5537).

Results

From 2001 to 2013, 1,396 new cases of leprosy were reported in Mossoró, RN, of which 55.4% were among women, 48.9% were MB, 9.7% were among children less than 15 years old, and 19.1% were among the elderly (60 or more years) (Table 1).

Table 1. Epidemiological indicators of leprosy in Mossoró, RN (2001–2013)

<table>
<thead>
<tr>
<th>Year</th>
<th>Number of New Cases</th>
<th>NCDR</th>
<th>Sex Ratio (M/F)</th>
<th>Age group</th>
<th>Women</th>
<th>MB</th>
<th>Grade 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt; 15</td>
<td>≥ 60</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2001</td>
<td>73</td>
<td>33.9</td>
<td>0.8</td>
<td>2.7</td>
<td>21.9</td>
<td>57.5</td>
<td>49.3</td>
</tr>
<tr>
<td>2002</td>
<td>101</td>
<td>46.2</td>
<td>0.9</td>
<td>11.9</td>
<td>13.9</td>
<td>55.4</td>
<td>56.4</td>
</tr>
<tr>
<td>2003</td>
<td>74</td>
<td>33.6</td>
<td>1.1</td>
<td>8.1</td>
<td>12.2</td>
<td>48.6</td>
<td>48.6</td>
</tr>
<tr>
<td>2004</td>
<td>106</td>
<td>47.6</td>
<td>0.8</td>
<td>11.3</td>
<td>20.8</td>
<td>58.5</td>
<td>46.2</td>
</tr>
<tr>
<td>2005</td>
<td>211</td>
<td>92.8</td>
<td>0.6</td>
<td>12.8</td>
<td>17.5</td>
<td>63.0</td>
<td>38.4</td>
</tr>
<tr>
<td>2006</td>
<td>111</td>
<td>48.3</td>
<td>0.8</td>
<td>9.9</td>
<td>24.3</td>
<td>58.6</td>
<td>48.6</td>
</tr>
<tr>
<td>2007</td>
<td>160</td>
<td>68.9</td>
<td>0.9</td>
<td>12.5</td>
<td>12.5</td>
<td>55.6</td>
<td>50.6</td>
</tr>
<tr>
<td>2008</td>
<td>101</td>
<td>41.8</td>
<td>0.9</td>
<td>9.9</td>
<td>20.8</td>
<td>55.4</td>
<td>58.4</td>
</tr>
<tr>
<td>2009</td>
<td>75</td>
<td>30.7</td>
<td>1.1</td>
<td>5.3</td>
<td>22.7</td>
<td>50.7</td>
<td>49.3</td>
</tr>
<tr>
<td>2010</td>
<td>91</td>
<td>35.4</td>
<td>0.7</td>
<td>4.3</td>
<td>19.6</td>
<td>59.8</td>
<td>48.9</td>
</tr>
<tr>
<td>2011</td>
<td>87</td>
<td>33.0</td>
<td>1.4</td>
<td>2.3</td>
<td>17.2</td>
<td>42.5</td>
<td>43.7</td>
</tr>
<tr>
<td>2012</td>
<td>109</td>
<td>40.5</td>
<td>1.2</td>
<td>8.3</td>
<td>25.9</td>
<td>47.2</td>
<td>57.4</td>
</tr>
<tr>
<td>2013</td>
<td>97</td>
<td>35.0</td>
<td>0.9</td>
<td>17.5</td>
<td>22.7</td>
<td>54.6</td>
<td>48.5</td>
</tr>
</tbody>
</table>

NCDR: New Case Detection Rates per 100,000 residents. Sex ratio: quotient of NCDR in men to NCDR in women. MB: multibacillary cases.

(*) Data not available. Brazilian Ministry of Health recommends that the percentage of cases with Grade 2 disability should only be calculated when the disability assessment proportion is greater than or equal to 75%. Source: SINAN/SES-RN; IBGE.

E T H I C A L  C O N S I D E R A T I O N S

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Results

From 2001 to 2013, 1,396 new cases of leprosy were reported in Mossoró, RN, of which 55.4% were among women, 48.9% were MB, 9.7% were among children less than 15 years old, and 19.1% were among the elderly (60 or more years) (Table 1).

Figure 1. General mean new case detection rates, and NCDR according to the operational classification, by age group, by 100,000 residents. Mossoró, RN, Brazil (2001–2013). NCDR: New Cases Detection Rates. PB: Paucibacillary; MB: Multibacillary. Source: SINAN/SES-RN; IBGE.
The NCDR increased with age at diagnosis, reaching a peak at 60–79 years, which reflects the NCDR of the MB cases (Figure 1).

Similarly, the percentage of MB cases increased with age: from 15% among children 0–14 years old to the maximum value of 74% among the elderly of 80 years old or older (Figure 2).

Of the 27 areas of Mossoró, 14 (52%) presented MB leprosy with a mean NCDR above 10 per 100,000 residents. It is worth noting two neighbourhoods with hyperendemic levels called “Santo Antônio” and “Belo Horizonte” (Figure 3).

During home visits, 531 (80%) elderly residents of Belo Horizonte were located and invited to participate in the study. Of these, 504 volunteers performed the ML Flow test.
<table>
<thead>
<tr>
<th>Sex</th>
<th>Age</th>
<th>ML Flow</th>
<th>Years of residence in the municipality</th>
<th>Skin lesions</th>
<th>Peripheral nerves</th>
<th>Anesthetic hands and/or feet</th>
<th>BI</th>
<th>Biopsy</th>
<th>PCR (Number of genome copies)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>72</td>
<td>4+</td>
<td>50</td>
<td>Present</td>
<td>Enlarged</td>
<td>Present</td>
<td>4.75</td>
<td>LL</td>
<td>Positive (71)</td>
</tr>
<tr>
<td>Male</td>
<td>77</td>
<td>4+</td>
<td>77</td>
<td>Absent</td>
<td>No alteration</td>
<td>Absent</td>
<td>0.75</td>
<td>BL</td>
<td>Negative</td>
</tr>
<tr>
<td>Male</td>
<td>72</td>
<td>3+</td>
<td>48</td>
<td>Absent</td>
<td>No alteration</td>
<td>Absent</td>
<td>0.0</td>
<td>No alteration</td>
<td>Positive (16)</td>
</tr>
<tr>
<td>Female</td>
<td>66</td>
<td>4+</td>
<td>33</td>
<td>Absent</td>
<td>No alteration</td>
<td>Absent</td>
<td>0.0</td>
<td>No alteration</td>
<td>Negative</td>
</tr>
</tbody>
</table>

(188 men and 316 women). The results were positive in five individuals (three men and two women). One female participant, with no signs of leprosy, had an ML Flow result of 1+ and was just provided with orientation regarding the disease. The results of the other four participants are presented in Table 2.

The two cases with positive bacillary loads and histopathological findings conclusive for leprosy started treatment with MDT/MB.

Discussion

The study confirms that Mossoró, RN is a highly endemic area of leprosy according to national parameters with an annual NCDR above 30 per 100,000 population in the period studied. Important increases in detection can be seen in years with intense diagnostic campaigns such as 2005. It is worrying to observe that in three of the eleven years studied, the percentage of new cases with disability Grade 2 was greater than or equal to 10%, including in 2005 despite increased detection.

Unlike the patterns observed during periods of decline of leprosy, the epidemiological indicators suggest active transmission of the disease in the municipality with a high percentage of new cases among children, greater NCDR among women, percentage of MB cases around 50% and percentage of elderly around 20% without an established trend. In this context of high endemicity, it is surprising that the mean NCDR peaked among the 60–79 year olds reflecting the detection of MB cases in this age group. Furthermore, the percentage of MB cases progressively increased during the lifespan reaching a maximum value among those of 80 years old or older. These results inspired the active case-finding strategy in 2016, which also obtained interesting results.

The association between MB leprosy and the elderly is discussed in the literature only in studies conducted in areas of decreasing endemicity. It was observed in Norway, the United States of America, Portugal and Japan that after the interruption of leprosy transmission, the detection of new cases continues for some time yet with an increase in the mean age of the new cases, a relative increase of new cases with MB leprosy and a higher percentage of cases among elderly people. The authors attribute these changes to the longer incubation period of MB leprosy that keep on arising in people who were infected many years earlier.

However, in Mossoró, the disease transmission remains active which lead to the hypothesis that the association between MB leprosy and the elderly may be a characteristic of the disease regardless of decreasing endemicity. It is noteworthy that with increasing age there is a process of immunosenescence and metabolism switches which decreases vaccine efficacy, slows the healing process of wounds, hampers the protection against microorganisms and increases the incidence of diseases such as osteoporosis and cancer. Monocytes and macrophages have reduced phagocytic capacity and production of reactive oxygen and nitrogen intermediates; furthermore, there is reduced expression of MHC molecules, essential for antigen presentation. The relationship between CD4 and CD8 T cells is reversed and there is a shift in the profile of cytokines from the Th1 profile to Th2 after T lymphocyte activation. Thus, all stages of individual mechanisms of defense against M. leprae seem to be weakened with aging.

The incidence of leprosy seems to be always greater among the elderly than younger populations except when there is a low life expectancy. In Norway, the greatest detection was among 15–29 year olds when the life expectancy in Europe was only 36-3 years; however,
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at the end of the 19th century, when life expectancy had increased to 50 years, the greatest incidence arose to this same age group.\textsuperscript{21–23} In the Republic of Congo, the greatest detection was registered among 30–39 year olds from 1957 to 1958\textsuperscript{24} with life expectancy at 41 years in 1960.\textsuperscript{25} In Mexico, the greatest NCDR was registered among 60–79 year olds\textsuperscript{26} when life expectancy increased from 70-4 years to 76-5 years from 1989 to 2009.\textsuperscript{25} In Korea the greatest detection was among 70–89 year olds\textsuperscript{27} with life expectancy increasing from 63-2 in 1973 to 81-5 years in 2013.\textsuperscript{25} No information was found regarding life expectancy in the Philippines from 1933 to 1940 when the greatest incidence of leprosy was registered among children 10–14 years old and 15–20 year olds;\textsuperscript{28} however, generally in Asia the life expectancy was only 28-6 years in 1913 and increased to 41-6 years in 1950.\textsuperscript{22} Furthermore, recent studies in Mexico and in the Republic of Korea during successive periods of decline in transmission showed that during the periods of greatest transmission, peak detection already occurred among the elderly.\textsuperscript{26,27}

No other publication was found regarding active case-finding of leprosy in the elderly; yet, the detection rates obtained in our study of 0-4% of MB leprosy among this population is alarming. Among elderly men, the detection rate was 1% (2/188). The case of BL leprosy without cutaneous lesions was surprising. The patient was examined by two experienced leprologists and no signs of leprosy were found, except questionable infiltration in the frontal region but bacillary loads were negative in both earlobes.

It is known that the immune system can protect an individual from the harmful effects of infectious diseases through mechanisms of immunological tolerance, a defence strategy, which reduces the negative effects on the host without affecting the parasite load,\textsuperscript{29} a probable explanation for this case. Interestingly, Cochrane in 1934 said that leprosy “is closely analogous to tuberculosis in many respects; but the causative organism is peculiar in that, though it is a parasite, it seems in many instances to establish an almost perfect commensalism with the tissues. This is illustrated by the type of case, not infrequently seen, in which there is little clinical evidence of the infection, but on examination innumerable bacilli are found wherever a scraping is taken; a balance seems to have been reached between the body and the bacillus whereby the latter lives and multiplies but causes little or no damage to the host”\textsuperscript{30}.

Serology is possibly a useful tool to identify these cases. Although large-scale serological surveys may not be appropriate for disease control,\textsuperscript{8,31} and recent publications have shown contradictory results for sensitivity and specificity of serological tests among contacts of leprosy cases.\textsuperscript{32,33} Nevertheless, one must emphasise that although we have found only 1% of ML Flow positivity among the elderly, no other serological study showed that 80% of seropositive individuals reacted strongly, which may be a characteristic of this age group in leprosy endemic areas.

The significance of the two participants with strong positive serology and positive PCR, but negative skin smears and no histological changes which confirm diagnosis of leprosy is not fully understood. However; this could be an early diagnosis of MB leprosy, before bacillary multiplication reached levels detectable on the skin smear, or these could be individuals who carry the bacilli but do not develop disease or an atypical MB leprosy presentation. These participants were counseled regarding the clinical manifestations of leprosy and will be reviewed every 6 months.

Currently, while there are a growing number of scientific papers\textsuperscript{1,2} and documents\textsuperscript{34} questioning the impact of MDT on leprosy transmission globally, we believe that control programmes must actively seek cases of MB leprosy. The biggest challenge may be
individuals in which multiplication of \textit{M. leprae} occurs without or with practically unnoticeable clinical manifestations. The frequency of this phenomenon and the possibility that it may be more common among the elderly are important questions that may bring new knowledge about leprosy and possibly help in the control of this endemic disease.

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**References**


