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Original Article

Development and Evolution of Nerve Damage in Individuals with Leprosy during Medical Treatment, at Completion of MDT and After Release from Treatment

GL Lopes[1], MGL Borges[2], AO Conceição[3], KNM Batista[4], GMM de Macedo[5], MB Xavier[6]

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Nerve damage in leprosy is related to the appearance of disabilities, the worst sequel of the disease. This study's objective was to study the evolution of nerve damage and estimate the risk of development of disabilities, during the medical treatment, as well as after completion of treatment and during post treatment follow-up. A cohort study was conducted, during period of 2006 to 2014, involving 85 new leprosy cases, treated in a reference service centre of leprosy. Data was collected from medical records and control books from the centre. The cases with or without nerve damage at the time of leprosy diagnosis were studied during treatment (three months after MDT was started), at the time of completion of MDT and one year after release from treatment for evolution of nerve damage. It was observed that in most (60/85) cases of this cohort, at the time of diagnosis of the disease clinical signs of nerve damage were present. There was predominance of a moderate stage of the sensory damage that did not decrease even at the end of the treatment and post treatment follow-up. It was observed that multibacillary cases had a higher risk of deterioration and or development of nerve damage. Cases with leprosy reactions showed higher risk of developing new nerve damage after completion of treatment and during the follow-up after release from treatment. In some cases the nerve damage was also aggravated during treatment. The presence of neuritis, during presentation and treatment increased the risk of worsening of the neural status. It was a observed that cases with more severe sensory damage and also those having disabilities at discharge presented a greater risk rate of deterioration and worsening of nerve damage up to one year after release from treatment. It is concluded that some factors like presence of nerve damage at the time of diagnosis, reactions and neuritis and MB classification are associated with increased risk of development and/or aggravation of nerve damage, emphasizing the importance of the proper monitoring of leprosy cases during treatment and also in the follow up period after completion of treatment.

Keywords : Leprosy, Neuropathy, release from treatment, reactions, physical disability

[1] GL Lopes, MD, Núcleo de Medicina Tropical, Universidade Federal do Pará, Brazil.
[2] MGL Borges, MD, Núcleo de Medicina Tropical, Universidade Federal do Pará, Brazil.
[3] AO Conceição, MD, Núcleo de Medicina Tropical, Universidade Federal do Pará, Brazil.
[4] KNM Batista, DD, Department of Physiotherapy, Universidade Federal do Pará, Brazil.
[5] GMM de Macedo, MD, Núcleo de Medicina Tropical, Universidade Federal do Pará, Brazil.
[6] MB Xavier, DD, Research Coordinator, Multidisciplinary Research in Dermatology and Tropical Hansenology, Universidade Federal do Pará, Brazil.

Correspondence to: Dr GL Lopes **Email:** geovanna.fisio@gmail.com

Introduction

Leprosy is an infectious mildly contagious disease, which has a slow and varied evolution, and whose clinical manifestations are related to the individual's immunologic response to the pathogen (Ministério da Saúde do Brasil 2010, 2002). It presents usually with dermatologic and neurologic manifestations, in which the neural component may be preponderant, although the cutaneous lesions are more evident and, in most cases, leads to disease diagnosis (Briton and Lockwood 2004). The neural involvement is intrinsically related to the cause of physical disabilities and deformations in leprosy, and therefore, nerve damage is considered to be the most important and alarming aspect of the disease. It is also the main cause of permanent physical disability caused by a mycobacterium in the world (Van Brakel et al 2012).

It is estimated that three million people in the world have some degree of physical disability due to leprosy and in approximately half of them it is of the severe type. Future projections estimate that about five million new cases can occur between 2000 and 2020 globally, and in 2020 it is believed that there will be an estimated one million leprosy cases with grade 2 disability (WHO 2010). For achieving a better outcome, the main trigger(s) for development of disabilities, in leprosy should be identified. This damage can be present at the time of leprosy diagnosis, during its treatment, and also during post treatment follow-up after discharge from Multi Drug Therapy (MDT). This can help in early diagnosis and prevention of permanent disabilities in leprosy patients (Gonçalves et al 2008).

The implementation MDT for the treatment of leprosy, in the last decades, has lead to the cure of thousands of individuals and preventing a large number of disabilities besides, helping to control the disease world wide (Ministério da Saúde do Brasil, 2005). However, MDT alone does not necessarily always prevent development and/or evolution of nerve damage. The risk of development and evolution of leprosy nerve damage was investigated in a cohort of leprosy patients attending the leprosy treatment centre from 2006 to 2014. The observations were analysed at leprosy diagnosis, during medical treatment, at the time of completion of MDT and a year after discharge and release from MDT.

Materials and Methods

It is a clinical observational study, in the involving a cohort of leprosy patients who attended Reference Clinic of Tropical and Infectious Diseases, at the Núcleo de Medicina Tropical of the Universidade Federal do Pará (NMT/UFPA), located in Belém, Pará state, Brazil during the period 2006 to 2014. The medical records, control books and register of patients with the diagnosis of leprosy were reviewed in the study.

Patients who fulfilled the following inclusion criteria were included: (i) new cases of leprosy, diagnosed and treated in consonance with policy of Brazil – six month fixed duration treatment (FDT) for paucibacillary (PB) and 12 months duration FDT for multibacillary (MB) cases as per Ministério da Saúde do Brasil recommendations (Ministério da Saúde do Brasil 2002), that were admitted in the service from January 2006 and until December 2014, patients from both the genders were included; Written informed consent was obtained from all patients who accepted to participate voluntarily in the study. Exclusion criteria included patients co-infected with HIV, suffering from AIDS, tuberculosis, HTLV (Human T cell leukemia-lymphoma virus), hepatitis etc were excluded from the study. Data of participants who fulfilled the inclusion and exclusion criteria were collected, and analysed in the study. The socio-demographic and clinical details of the patients were noted. Sensory

and/or sensorimotor impairments in the hands and/or feet were measured and nerve damage was assessed at the time of diagnosis, during MDT, and/or a year after discharge from treatment (Garbino 2000). Through the evaluation of the sensitivity in hands and feet with the Semmes-Weinstein monofilaments, the presence of clinical data that allow the classification of the case from stage 2 was considered as sensory damage (it means not feeling the monofilament 0.2 grams - blue color - hands and 2 grams - lilac color - on the feet) indicating decreased protective sensitivity. Sensory alteration gradient was measured by using Semmes-Weinstein monofilaments. The worsening or improvement in sensitivity impairment was determined and recorded as increased or decreased, graded in stages (stages 1-5), according to the sensitivity change gradient (Table 1).

Through the evaluation of the motor function of limb-specific muscles with the VMT technique, the degree of muscle strength was measured to grade the extent of motor damage (Table 2).

The cases identified to have nerve damage at the time of leprosy diagnosis were studied during treatment (three months after MDT was started), at the time of completion of MDT and one year after release from treatment. In patients without nerve damage on diagnosis, nerve impairment evolution was studied in the same fashion and at similar time periods. Disabilities were graded as per Ministério da Saúde do Brasil (2010) criteria:

I) Grade 0: No problem with eyes, hands and feet Leprosy;

II) Grade 1: Decreased or lost sensation in the eyes; decrease or loss of protective sensitivity in hands and / or feet;

III) Grade 2: Eyes: lagophthalmus and/or ectropion; trichiasis; opac central corneal age; visual acuity less than 0.1 or inability to count fingers at 6m from distance; Hands: trophic lesions and/or traumatic lesions; garrat; reabsorption; Fallen hand; Feet: trophic and / or traumatic lesions; claws; reabsorption; foot drop; ankle contracture.

Table 1 : Sensory alteration gradient according to sensory involvement mapped by using Semmes-Weinstein monofilaments

Monofilament	Interpretation	Sensitive alteration gradient
0.05 grams	Sensibility considered normal for hands and feet	Stage 1
0.2 grams	Decreased sensibility in the hands, with difficulties as to fine discrimination	Stage 1*
	Considered "normal" to feet	Stage 2**
2.0 grams	Protective sensibility diminished, remaining enough to prevent injuries	Stage 2
4. 0grams	Loss of protective sensibility	Stage 3
10. 0grams	Loss of protective sensibility, still able to feel profound pressure and pain	Stage 3
300.0 grams	The sensibility to pressure and pain remains	Stage 4
Does not feel any sensation	Loss of the sensation of profound pressure, normally does not feel pain.	Stage 5

*: regarding feet evaluation; **: regarding hand evaluation

Table 2 : Motor alteration gradient measured by VMT technique

Strength Graduation	Interpretation	Functional condition
5	Movement with maximum resistance	Strong (normal)
4	Movement with partial resistance	Diminished
3	Complete movement without resistance	Diminished
2	Partial movement	Diminished
1	Muscular contraction without movement	Diminished
0	Paralysis without movement	Paralyzed

For the analysis of nerve damage, Cochran's Q-test was used for data analysis in the different time periods of evaluation i.e. at diagnosis, during treatment, at the time of discharge from treatment and at 1 year post- treatment follow-up. The Relative Risk (RR) realized risk estimation for the development and evolution of nerve damage was undertaken presuming a sampling error of $\alpha = 5\%$ and p value ≤ 0.05. The research was approved by the Ethics and Research Committee of the UFPA (protocol number 015568/2015).

Results

Out of the 85 studied cases, 59 (65.9%) were males and 26 (34.1%) were females, and 51 (60%) belonged to 24 to 59 years age group, average age was 32.7 ± 15.9. Among these 53 (62.3%) were MB patients, remaining 32 (37.7%) belonged to PB group, among these 46 (54.4%) presented with BB type. Leprosy reactions were presents in 31 (36.5%) of them, with preponderance 25/31 (80.6%) having type I reaction. 45 (52.9%) presented with neuritis. As for the Disability Grade (DG), 33 (38. 9%) presented some disability at the diagnosis, 14 of them (42.4%) had severe grade 2 disability. The frequency of cases admitted in the service with some DG 33 (38.9%) did not change until the end of the study (p: 0.3916/Cochran's Q-test).

Among the studied cases, 60/85 (70.6%) presented with clinical signs of nerve damage at the time of diagnosis, with the predominance of stage 2 at the beginning, as well as in the subsequent investigated period. The frequency of cases with nerve damage in the post-discharge period remained same as it was present at the time of diagnosis (p: 0.0893/Cochran's Q-test).

As for the 25/85 cases (29.4%) without nerve damage at diagnosis, 5 (20%) developed nerve damage until the third month after the starting MDT; 9 (36%) at medical discharge and 8 (32%) up to one year after discharge related to the diagnosis. For these 25 cases without nerve damage on diagnosis, cases classified as MB showed significantly higher risk to develop the nerve damage during treatment, with a risk rate 7.88 (1.56-12.29) (p: 0.0102) compared with PB group. At discharge and during post-discharge one year period, besides operational classification, the presences of reactions and neuritis have shown statistical relevance to the risk for the development of the outcome (Table 3). There were three cases with leprosy reactions and eleven with identified neuritis at discharge, all classified as MB.

Among the 60 (70.6% of the total 85 cases studied) cases having detectable/measurable nerve damage at diagnosis, in 11/60 (18.3%) the clinical condition deteriorated by the third month after the initiation of the medical treatment; in 13 (21.6%) up to time of completion of treatment and in 16 (26 %) up to one year after the discharge from treatment, number is accumulative, for

Table 3 : Development of nerve damage in 25 leprosy patients without any detectable nerve damage at time of diagnosis : during treatment, at completion of MDT and T follow-up after release from treatment

Variables	Development of nerve damage Yes N (%)	No (N (%)	RR (IC 95%)	p value*
During treatment				
Operational class			7.88	0.0102
PB	2(8)	19(76)	1.56-12.29	
MB	3(12)	1(4)		
Total	5(20)	20(80)		
Discharge				
Operational class			5.14	0.0028
PB	3(12)	15(60)	0.16-0.92	
MB	6(24)	1(4)		
Total	9(36)	16(64)		
Post-discharge				
Operational class			1.19	0.0047
PB	4(16)	17(68)	1.28-2.05	
MB	4(16)	**		
Total	8(32)	17(68)		
Discharge				
Reactions			3.67	0.0343
Presence	3(12)	**	2.22-4.15	
Absence	6(24)	16(64)		
Total	9(36)	16(64)		
Post-discharge				
Reactions			4.40	0.0211
Presence	3(12)	**	2.65-5.11	
MB	5(20)	17(68)		
Total	8(32)	17(68)		
Discharge				
Neuritis			10.18	0.0015
Presence	8(32)	3(12)	2.45-6.55	
Absence	1(4)	13(52)		
Total	9(36)	16(64)		
Post-discharge				
Neuritis			8.91	0.0050
Presence	7(28)	4(16)	1.28-62.05	
MB	1(4)	13(52)		
Total	8(32)	17(68)		

Table 4 : Evolution of nerve damage in 60 leprosy patients initially reporting with nerve damage : during treatment, at completion of MDT and during follow-up after release from treatment

Variables	Evolution of nerve damage Yes N (%)	No (N (%)	RR (IC 95%)	p value*
During of treatment				
Operational class			1.29	0.0455
PB	**	11(18.3)	1.11-1.50	
MB	11(18.3)	38(63.4)		
Total	11(18.3)	49(81.7)		
Discharge				
Operational class			1.36	0.0436
PB	**	11(18.4)	1.15-1.61	
MB	13(21.6)	36(60)		
Total	13(21.6)	47(78.4)		
Post-discharge				
Operational class			1.48	0.0332
PB	**	11(18.3)	1.22-1.80	
MB	16(26.7)	33(55)		
Total	16(26.7)	44(73.3)		
During of treatment				
Reactions			5.14	0.0122
Presence	9(15)	19(31.7)	1.21-21.83	
Absence	2(3.3)	30(50)		
Total	11(18.3)	49(81.7)		
During of treatment				
Neuritis			3.05	0.0467
Presence	8(13.3)	20(33.4)	1.89-10.39	
MB	3(5)	29(48.3)		
Total	11(18.3)	49(81.7)		

example patients who worsened by third month were not excluded from further analysis and so on. Among the cases with neural damage at diagnosis, 49 (81.7%) were MB, 28 (46.7%) presented reactions, 20 (71.4%) cases type I and 8 type II (28.6%). All cases with neural damage were appropriately treated and none deteriorated. MB cases of this study group had RR of 1.29 (p: 0.0455), cases with reactions had RR of 5.14 (p: 0,0122) and those with neuritis had RR of 3.05) (p:0.0467), this implied higher risk towards aggravation the nerve damage during treatment than those which did not have these problems. There were 28 cases with leprosy reactions, among them 18 developed nerve damage by the third month of MDT. At completion of treatment and release from MDT only the MB patients showed higher/greater risk for evolution, of nerve damage with a 1.36 (p:0.0436) and 1.48 (p: 0.0332) RR, respectively (Table 4).

In this study, it was also observed that cases with more severe sensory damage (from stage 3) at discharge presented a greater risk rate 1.69 (p: 0.0353) of deterioration and worsening of nerve damage up to one year after release from treatment. As for the development of disabilities and the grade of disabilities, it was observed that cases having disabilities at the time of diagnosis had a 3 times (p:0.0464) higher risk of deterioration of nerve damage up to time of completion of treatment, and 3.31 (p: 0.0216) up to one year of release from treatment.

Discussion

Leprosy is a treatable disease, despite its challenging course due to the exceptional incapacitating potential provoked by nerve damage. The higher prevalence of cases in males, during the economically active age group observed in this study is in line with that reported by others (Conceicao 2012, Malao et al 2011, Braga 2011, Rafael 2009, WHO 2009).

The observations of the leprosy nerve damage in most of cases suggested that there might have been delay in diagnosis and treatment. About 70% of the investigated cases have presented sensory damage at the first time of presentation at the service, and this remained un altered even after 1 year after completion of treatment (Table 4). Early diagnosis is one of the pillars for leprosy control, and in longer standing disease even the sensory changes may become irreversible as observed in this study, the majority of cases were first diagnosed with only stage 2 sensory damage but of long duration. It was observed that even sensory damage could not be reverted even after one year after completion of therapy in treatment at the Reference Service Centre which is manned by a multi-professional dedicated team that routinely attends to leprosy patients. This characterizes the chronic nature of leprosy disease which might have been aggravated probably, by late diagnosis.

The findings of this research related to leprosy nerve damage demonstrated that there are clinical exposure factors related to nerve injuries associated with the risk to develop and aggravate nerve damage during medical treatment, at the discharge and even after it.

MB disease, presence of neuritis and reactions were identified as important factors, contributing to the increased risk of development and aggravation of nerve damage in these leprosy patients (Table 3 and 4). The presence of neuritis and reactions showed higher risk both for the development of nerve damage during treatment, at completion of treatment and for aggravating the loss of neural function. It was also observed most neuritis episodes took place simultaneously with the reactions.

Gonçalves et al (2008) have reported that the occurrence of neuritis in leprosy patients tends to deteriorate the nerve damage as was observed during the subsequent follow-up of the cases. They also demonstrated that the first 12 months of attendance after diagnosis are the most important and crucial period for the control of neuritis, as there is a greater risk for the development and/or evolution of neural damage. It is also known and as reported in literature that neuritis can occur in some cases even after 24 months after initial diagnosis and treatment (Batista 2008).

In the patients initiated on MDT without nerve damage (Table 3), only 3/ 25 (12%) experienced reactions, up to discharge. In contrast, among the cases reporting with nerve damage at (Table 4), admission in the service, 28/60 (47%) manifested reactional episodes of which 18 of them experienced it at the time of diagnosis or during the three months after implantation of MDT. Higher

incidence of reaction episodes and neuritis in, perhaps, contributed for the greater risk of both development and aggravation of nerve damage, which may be sometimes severe, requires immediate intervention due to its potential towards developing and evolving nerve injury and even the disabilities (Scollard et al 2015).

The ordinance 3.125/2010 from Health Ministry of Brazil (Ministério da Saúde do Brasil 2010, WHO 2009) has guidelines, and draws attention to the control of leprosy in Brazilian territory, emphasizes that cases with reactions must be attended by experienced professionals from reference services, as the NMT/UFPA clinic, wherein probably the reaction and neuritis episodes can be controlled better. This would reduce the risks for the development and/or aggravating of nerve damage in the immediate follow-up period.

In the present study, MB cases showed a greater risk for the negative outcome of the study throughout the investigation period, possibly due to the high bacillary load in these patients that, may be associated with the inefficient immunologic cellular response to the infecting bacillus. This makes it more difficult to control the inflammatory process leading to the chronicity of the disease and of the nerve injury that, sometimes, progresses towards irreversibility; generating disabilities (Scollard et al 2006).

The aggravation of the nerve damage even after completion of MDT during the follow-up period in MB cases may be due to the persistence of bacillary fragments in the nerves, which, although dead are, still presenting as antigens that stimulates the immunological system of the host even years after the treatment has ended (Jacobson and Krahenbuhl 1999).

Lockwood and Saunderson (2012) have also stated that about 60% of MB patients are diagnosed with some degree of nerve damage and they tend to get worse frequently during on going treatment and even after completion of MDT. In a prospective cohort study, undertaken in Bangladesh, 2.510 leprosy patients were followed up for two years, in order to identify predictive factors of disability and worsening of nerve damage. The authors stratified their results in mild, moderate and severe risk groups for the outcome. MB patients with nerve damage throughout the follow-up time presented higher risk of deterioration even one year after discharge (Croft et al 2000). The present study also shows that cases with advanced stages of sensory damage had a higher risk in deteriorating or continued nerve damage in the follow-up period. This was despite care and expertise rendered by the multi-professional team. This suggests that immediate detection and intervention in the presence of nerve damage in milder stages is very important to arrest the nerve damage and prevent its deterioration. The chronic character of the disease also possibly complicates the recuperation, even after adequate interventions.

Previous disabilities also showed higher risk aggravating the nerve damage in the subsequent observation period, corroborating the findings with other reported studies (Conceicao 2009, Goncalves et al 2009, Nardi et al 2005, Pigmental et al 2002). In these studies, also, it was reported that the presence of disabilities at diagnosis was associated with the deterioration of these disabilities after completion of treatment and post treatment follow-up. The disabilities and deformities are one of the important causes of the stigma and isolation of leprosy patients in society (Imbriba et al 2009, Kerry-Pontes et al 2004), as also the Brazilian's Health Ministry

(Ministério da Saúde do Brasil 2008). This emphasizes the importance of preventing, controlling and treating the disabilities. Programme of rehabilitation, presently mainly localized in capital area of state (Ministério da Saúde do Brasil 2013) should be expanded to areas where it is needed most.

Leprosy being a complex disease, may not be so easy to treat. Identifying the cases with higher risk of getting nerve damage, as done in present study, will be helpful in developing monitoring and implementation strategies to prevent and /or effectively manage factors contributing to development of disabilities in leprosy.

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