Aus der Klinik für Gastroenterologie, Hepatologie und Infektiologie der
Heinrich-Heine-Universität Düsseldorf
Direktor: Prof. Dr. med. D. Häussinger

High occurrence of disabilities caused by leprosy: census from a hyperendemic area in Brazil

Dissertation

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Kathrin Christine Häfner
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Dekan: Prof. Dr. med. Nikolaj Klöcker
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Zweitgutachter: Prof. Dr. med. Colin R. MacKenzie

Zitat

„Weitermachen ist sinnlos, aber aufhören ist noch sinnloser. Also machen wir weiter!“

(Dr. Ruth Pfau)

Zusammenfassung

Lepra ist heutzutage vor allem in Entwicklungsländern und Schwellenländern anzutreffen. Durch Bemühungen der landesweiten Leprakontrollprogramme sinkt die weltweite Neuerkrankungsrate kontinuierlich. Lepra stellt jedoch nach wie vor ein Problem für das öffentliche Gesundheitswesen in Brasilien dar. Die Kontrolle und Reduktion dieser Krankheit wird durch Therapieunterbrechungen bzw. -abbrüche der *multidrug therapy* (MDT) sowie späte Diagnosestellung erschwert. Dadurch werden der Krankheitsverlauf gestärkt und Transmissionsursachen nicht beseitigt. Als Folge treten Behinderungen auf, die durch frühe Diagnosestellung sowie Einhaltung der MDT verhindert worden wären.
Wir führten Feldstudien in einer hyperendemischen Region im Norden Brasiliens durch. In 78 Bezirken des Bundesstaates Tocantins lagen für 1488 Personen Daten im zentralen Lepraregister der brasilianischen Gesundheitsbehörde (SINAN – *Sistema de Informação de Agravos de Notificação*) vor, die die Zielpopulation bildeten.
In einer ersten Studie wurde anhand einer klinischen dermatoneurologischen Untersuchung der Zustand der Augen, Hände und Füße von Leprapatienten entsprechend des WHO-Standards erfasst. Weiterhin wurden zusätzliche, bei den örtlichen Gesundheitsposten vorliegende Informationen aus den Patientenakten in die Studie aufgenommen. Insgesamt 910 Patienten mit einem Erstdiagnosezeitpunkt zwischen 2006 und 2008 wurden klinisch untersucht und befragt. Von den Teilnehmern mit vollständiger Dateninformation hatten 91,3% (783/858) die MDT abgeschlossen. Am häufigsten traten folgende klinische Befunde auf: 45,3% der Patienten wiesen vergrößerte/schmerzhafte Nerven bei der Palpation auf – v.a. *N. ulnaris* (22,7%), gefolgt von *N. tibialis posterior* (21,6%) und *N. fibularis* (20,5 %). Ein Verlust oder Reduktion der Sensibilität konnte bei 22,2% festgestellt werden, eine reduzierte motorische Nervenfunktion bei 20,4% der Probanden. Der prozentuale Anteil an Patienten mit *disability grade 1* (Grad 1-Behinderung - G1D) war zum Zeitpunkt der Diagnose mit 22,6 % (142/629) größer als zum Zeitpunkt der vorliegenden Studie mit 19,6% (178/910). Im Gegensatz dazu wurde zum Zeitpunkt der Studie bei 9,2% (84/910) der Probanden *disability grade 2* (G2D) diagnostiziert, zum Zeitpunkt der Diagnose bei 4,5 % (28/629). Männer zeigten ein höheres Vorkommen eines höheren Behinderungsgrads ($p<0,01$). Die Patienten mit G2D litten am häufigsten unter Krallenhänden (26/910; 2,9 %), plantaren Ulcera (23/910; 2,5%) sowie Hautabrasionen/Exkoriationen an den Füßen (12/910; 1,3%).
In einer zweiten Studie wurden aus der Zielpopulation 936 Patienten untersucht, um Therapieabbrüche und -unterbrechungen zu beschreiben und assoziierte Faktoren zu bestimmen. 147/806 (18,2%) der Patienten hatten im Verlauf der Behandlung die MDT mindestens zu einem Zeitpunkt unterbrochen. Die Unterbrechung war u.a. signifikant assoziiert mit beengten Wohnverhältnissen ($p=0,04$; OR=1,95) und mit Schwierigkeiten, die Tabletten einzunehmen ($p=0,02$; OR=1,66).
Es konnte gezeigt werden, dass mit Lepra verbundene Behinderungen im Untersuchungsgebiet weit verbreitet sind. Therapieabbrüche sind mit Faktoren assoziiert, die durch das Leprakontrollprogramm systematisch angegangen werden können. Es ist notwendig, dass das Gesundheitssystem die intensive Weiterbetreuung der Patienten auch nach Ende der primären Behandlungsphase (MDT) in die Gesundheitsversorgung integriert. Aufgrund des erhöhten Risikos bei Männern sollte im Rahmen der Leprakontrolle besonders auf die Männer eingegangen werden. Ein integrierter Ansatz ist notwendig, der die klinische Kontrolle der Patienten beinhaltet, Medikamente zur besseren Einnahme verwendet und über einen längeren Zeitraum auch noch nach Therapieabschluss die Nachsorge der Patienten sichert.

Summary

Especially in low- and middle-income countries, leprosy is still an endemic disease. In recent years, as a result of systematic leprosy control measures the new case detection rate continuously has been reduced worldwide. However, leprosy is still a public health problem in Brazil. The control and reduction of this disease are hampered by the interruption/defaulting of multidrug therapy (MDT), and by late diagnosis. Consequently, there is disease progression, and active transmission. As a result, physical disabilities occur, which could have been prevented by early diagnosis and compliance to MDT.

We performed field studies in a hyperendemic area in the central Savannah region in Northern Brazil. In the central register of the Brazilian disease control system (SINAN), there were 1488 confirmed leprosy cases from 78 districts in Tocantins state, which were defined as the target population.

The impairments of eyes, hands and feet of leprosy patients were assessed in a first sub-study, based on clinical examinations according to WHO definitions of disability grading. Furthermore, secondary data of patient records were collected at local health care centres. A total of 910 patients, newly diagnosed with leprosy between 2006 and 2008, were clinically examined and interviewed. 91,3% (783/858) of participants with complete information had finished MDT. The following clinical findings were most commonly observed: 45,3% of patients with enlarged/painful nerves, especially the ulnar nerve (22,7%), followed by the tibial nerve (21,6%) and fibular nerve (20,5%); 22,5% with loss or reduction of sensibility; and 20,4% with reduced motor function. The proportion of participants with disability grade 1 (G1D) was at diagnosis higher (22,6% 142/629) at diagnosis than at the moment of the study (19,6 %; 178/910). A total of 9,2% (84/910) of the participants presented with G2D at the moment of our study, in contrast to 4,5% (28/629) at diagnosis. Male participants presented with higher GD than women ($p<0,01$). Patients with G2D mostly suffered from claw hands (26/910; 2,5%), plantar ulcers (23/910; 2,5%) and abrasion/excoriation on feet (12/910; 1,3%)

In the second sub-study, 936 patients were examined to describe defaulting and interruption of MDT and to identify associated factors. 147/806 (18,2%) of the participants had interrupted MDT at least once. The interruption was i.a. significantly associated with crowded housing conditions ($p=0,04$; OR=1,95) and with difficulties in swallowing MDT drugs ($p=0,02$; OR=1,66).

The studies show that leprosy-associated disabilities are still common in the study area. Interruption and defaulting of MDT are associated with modifiable factors, which can be systematically addressed by the leprosy control programs. It is necessary that the health care system also integrates intensive follow-up of patients after discharge from treatment. Considering the higher risk in males, leprosy control should particularly focus on males. An integrated approach is needed, including clinical care of patients, use of tablets which are more easily to take, and follow-up of patients for a prolonged period, even after discharge from MDT.

Abkürzungsverzeichnis

BB	borderline Lepra
BCG	Bacillus Calmette-Guérin
BL	borderline lepromatöse Lepra
BT	borderline-tuberkuloide Lepra
DOT	*directly observed treatment*
ENL	Erythema nodosum leprosum
G0D/G1D/G2D	*grade of disability* 0 /1 / 2
GD	*grade of disability*
Integrahans MAPATOPI	eine vom brasilianischen Forschungsausschuss finanzierte sowie von der Universität Fortaleza durchgeführte Studie über Lepra in den Bundesstaaten Maranhão, Pará, Tocantins und Piauí im Cluster 1
LL	lepromatöse Lepra
M.	Mycobacterium
MB	multibazilläre Lepra
MDT	*multidrug therapy*
N.	*nervus*
PB	paucibazilläre Lepra
PNL	*pure neural leprosy*
RFT	*release from treatment*
SINAN	*sistema de informação de agravos de notificação (Nationales System für meldepflichtige* Erkrankungen)
TT	tuberkuloide Lepra
WHO	*World Health Organisation*

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1 Einleitung

1.1 Epidemiologie und Kontrolle der Lepra

Lepra ist eine der ältesten Infektionserkrankungen der Menschheitsgeschichte, die vor allem mit sozialer Ausgrenzung und dem Verlust von Gliedmaßen in Verbindung gebracht wird. In der westlichen Welt ist nur wenigen Menschen bekannt, dass Lepra weiterhin in vielen Entwicklungsländern ein aktuelles Thema der Gesundheitspolitik ist.

Vor allem Indien wird mit einer großen Anzahl an Lepraerkrankungen assoziiert. Dabei betrifft das Vorkommen der Lepraerkrankung nicht nur die südostasiatischen Länder, sondern auch afrikanische und lateinamerikanische Länder. In Europa konnte durch Verbesserung der hygienischen Verhältnisse und der Gesundheitsversorgung sowie durch Beginn der antibiotischen Therapie bereits seit Ende des 19. Jahrhunderts die Anzahl der Lepraerkrankungen deutlich gesenkt und bis Mitte des 20. Jahrhunderts ausgerottet werden. Laut WHO belief sich 2016 die Anzahl an Lepraneuerkrankungen in Deutschland auf 2, in den Niederlanden auf 5, in Portugal auf 4 und in Italien auf 12, wobei nur ein Patient aus Italien auch in Italien geboren wurde [1]. Die anderen Leprapatienten waren Touristen oder Immigranten aus endemischen Ländern.

Um weiterhin die Anzahl der Leprapatienten zu senken und dem Ziel der Ausrottung der Lepra näher zu kommen, wird die *multidrug therapy* (MDT) seit 1995 von der WHO propagiert und steht den Leprapatienten durch Spenden der Novartis *Foundation* [2, 3] kostenlos zur Verfügung .

Heutzutage ist Lepra vor allem in den Entwicklungsländern und Schwellenländern wie Indien, Bangladesch, die Demokratische Republik Kongo sowie Brasilien anzutreffen. Trotz der hohen absoluten Anzahl an Erkrankungen wird Brasilien im Vergleich zu den anderen Ländern eher selten mit Lepra in Verbindung gebracht. Mithilfe von regelmäßig optimierten Lepra-Kontrollprogrammen und Kampagnen werden nationale und internationale Bemühungen betrieben, um eine weitere Ausbreitung der Erkrankung zu verhindern und das Ziel einer endgültigen Ausrottung zu erreichen.

Im Lepra-Update der WHO mit den aktuellsten Daten von 2017 [4] wird dargestellt, dass im Zeitraum von 2007 bis 2017 die Anzahl der Neuerkrankungen von Lepra weltweit von 258 133 auf 210 671 Neuerkrankungen pro Jahr reduziert wurde. Im Jahre 2017 wurden 92,4% (26 875/29 101) aller Lepraneuerkrankungen des amerikanischen Kontinents in Brasilien registriert. Indien (126 164), Brasilien (26 875) und Indonesien (15 910) waren die einzigen Länder, deren Anzahl an Neuerkrankungen mehr als 10.000 betrug. Zudem konnte in Äthiopien (von 6,9 % auf 12,9 %), in der Demokratischen Republik Kongo (von 11% auf 14,2 %), in Indien (von 3 auf 3,6 %) und in Brasilien (von 6,5 auf 7,3 %) von 2011 bzw. 2012 bis 2017 ein wachsender prozentualer Anteil am höchsten Behinderungsgrad 2 (G2D, *grade 2 of disability* – nähere Erläuterungen zu den GDs unter dem Kapitel 1.2.5) festgestellt werden.

Ein Grund für die weltweite Reduktion von Lepraneuerkrankungen ist eine Verbesserung in der Etablierung des von der WHO propagierten Leprakontrollprogramms, welches in den „*Operational Guidelines*“ der WHO zu finden ist. Hier werden die aktuellen Probleme und Lücken in der Leprakontrolle mithilfe der weltweiten Studiendaten untersucht, um regelmäßig eine Anpassung der weltweiten Richtlinien im Kampf gegen die Lepra zu erzielen [5-7]. Nationale Gremien überarbeiten die Richtlinien und integrieren sie in ihr nationales Leprakontrollprogramm.

In Brasilien werden die meisten Lepraerkrankungen vor allem in den ärmeren Regionen wie dem Norden, Nordosten oder dem Amazonasgebiet verzeichnet. Dort ist die gesundheitliche Versorgung aufgrund der schlechten Infrastruktur und der weit verstreut angesiedelten Bevölkerung am schlechtesten.

Das brasilianische Gesundheitsministerium hat 1993 eine Datenbank entworfen, in der Patienten mit meldepflichtigen Krankheiten wie Lepra, Cholera, Tuberkulose und anderen Erkrankungen gespeichert werden [8]. Auf die weiterhin bestehende hohe Anzahl an Lepraerkrankungen reagierte das Brasilianische Gesundheitsministerium, indem es Daten von 2005 bis 2007 zu Lepraneuerkrankungen aus dem nationalem Melderegister, dem *„sistema de informação de agravos de notificação“* (SINAN) analysierte. SINAN ist eine nationale Datenbank, in der meldepflichtige Erkrankungen registriert werden. Anhand dieser Daten wurde Brasilien in zehn Hochrisikoregionen für Lepra, sog.

Cluster, eingeteilt, die die Regionen mit den höchsten Transmissionsraten repräsentierten. Die zehn Cluster deckten nur 17,5% der brasilianischen Bevölkerung ab, verzeichneten aber in den Jahren 2005 bis 2007 mehr als die Hälfte (53,5%) der neu entdeckten Lepraerkrankungen in Brasilien.

Da die allgemeine Informationslage zu der aktuellen Leprasituation unvollständig war, sollten Studien, die vom Gesundheitsministerium unterstützt wurden, diese Datenlücken in den Hochrisikoclustern füllen und die komplexen Ursachen der hier weiterhin bestehenden hohen Transmissionsrate aufdecken.

An der Bundesuniversität von Ceará in Brasilien wurde 2009 die interdisziplinäre Studie Integrahans MAPATOPI ins Leben gerufen [9], welche epidemiologische, klinische, psychosoziale und operative Muster von Lepra in Teilen der Bundesstaaten Maranhão, Pará, Tocantins und Piauí ergründen soll. Beide Publikationen dieser Dissertation sind Teil dieser Studie. Die Feldstudien fanden in dem logistisch am besten zu erreichenden Teil des Clusters 1 im Bundesstaat Tocantins statt.

Durch Erlangung von unterschiedlichen Informationen sollte eine gute Deskription eines Patientenkollektivs aus einem Gebiet mit hoher Transmissionsrate erlangt werden. Mithilfe dieser Informationen sollen Missstände und Ursachen für die weiterhin hohe Transmissionsrate detektiert werden, so dass das Brasilianische Gesundheitsministerium mit den erhobenen Daten Strategien und Lösungen entwickeln kann, um das nationale Leprakontrollprogramm zu optimieren. Somit will man dem Ziel der kontinuierlichen Reduktion von neu diagnostizierten Lepraerkrankungen bis hin zur Elimination der Lepra in Brasilien näherkommen.

Bei Häfner et al. (2017) wurde der Schwerpunkt auf die Lepra-assoziierten physischen Behinderungen gelegt. Hierbei geben die Untersuchungsergebnisse der körperlichen Untersuchung von Leprapatienten einen Überblick über den Krankheitszustand der Probanden zum Zeitpunkt der Datenerhebung. Zudem wurden die erhobenen Behinderungsgrade (*grade of disability - GD*) mit denen am Tag der Diagnosestellung verglichen, um die Dynamik dieser zu sehen. Da die meisten Probanden zum Zeitpunkt der Datenerhebung bereits die MDT beendet hatten, konzentrierte man sich auf die Zeit nach Beendigung der Therapie.

Die zweite Publikation von Heukelbach et al. (2011) fokussierte sich auf das Patientenkollektiv, welches die MDT unterbrochen oder abgebrochen hatte. Dabei wurden die psychosozialen, epidemiologischen sowie klinischen Faktoren, die zu einem Therapieabbruch führten, näher beleuchtet.

1.2 Die Erkrankung Lepra

Da Lepraerkrankungen in Deutschland bzw. Europa eine Seltenheit sind und oftmals im medizinischen/gesundheitlichen Bereich die Basiskenntnisse nur rudimentär vorhanden sind, soll im Folgenden ein kurzer Überblick über die Erkrankung Lepra erfolgen.

1.2.1 *Mycobacterium leprae*

Ursache für die Lepraerkrankung ist *Mycobacterium leprae*, welches 1873 von dem Norweger G. H. Armauer Hansen entdeckt wurde. Es ist ein säurefestes, gram-positives, stäbchenförmiges und obligat intrazelluläres Bakterium, das sich vorwiegend in den Histiozyten der Haut, der Schleimhaut und den Schwann'schen Zellen der peripheren Nerven vermehrt [10].

Neben dem menschlichen Gewebe dienen weitere z. B. Mäusefüße und Neunbinden-Gürteltiere als Reservoire für *M. leprae*.

1.2.2 Transmission, Infektiosität und Pathogenese

Der genaue Transmissionsweg von *M. leprae* konnte aufgrund der fehlenden *in vitro*-Kultivierbarkeit bisher noch nicht gänzlich geklärt werden. Nach einer Studie von 1977 [11] wurde die Tröpfchenübertragung als eine weitere Hypothese zur bisher gängigen Meinung der Infektion per Hautkontakt ins Spiel gebracht. Als die wichtigsten Eintrittspforten in den menschlichen Körper gelten Haut und Schleimhaut - vor allem die Schleimhaut des Respirationstraktes.

Neben der Bakteriendosis – paucibazillär (PB) versus multibazillär (MB) - spielt die Reaktion des Immunsystems sowie die Zeitdauer des Kontaktes mit einer lepraerkrankten Person eine wichtige Rolle bei der Infizierung mit Lepra und für den klinischen Verlauf der Erkrankung.

Aufgrund der langsamen Teilung (10-14 Tage) kann die Inkubationszeit sehr variabel (bis zu 30 Jahre) sein, jedoch liegt sie in der Mehrzahl der Erkrankungen bei drei bis fünf Jahren.

Dringen *M. leprae* in den menschlichen Körper ein, gelangen sie durch Makrophagen in die Schwann'schen Zellen der peripheren Nerven und Epithelzellen der Schleimhäute und Haut. Diese verlieren die Fähigkeit, die schützende Myelinscheide der Nerven zu bilden. Dadurch wird die sensible, motorische und autonome Funktion der Nerven geschädigt, was zu Hypohidrose, Paralyse und Anästhesie in den jeweiligen Innervationsgebieten führen kann. Bei ausbleibender adäquater Therapie der Erkrankung und ihrer Komplikationen wie Lepra-Reaktionen können persistierende Nervenläsionen zur Ausprägung von körperlichen Behinderungen und Deformitäten der Extremitäten führen.

Die Übertragung der multibazillären Lepra ist von der jeweiligen Immunkompetenz des betroffenen Individuums abhängig. Etwa 95 % der Menschen entwickeln eine ausreichende Immunantwort gegen die Bakterien, so dass diese eine subklinische Infektion ohne typische Leprasymptome ausbilden, aber potenzielle Überträger sein können [10]. Liegt bei engem Leprakontakt keine natürliche Resistenz vor, entscheidet die Immunitätslage der Patienten über die sich entwickelnde Lepraform. Daher wird Lepra auch als eine Spektrumkrankheit bezeichnet. Ridley und Jopling führten 1966 ein Klassifikationssystem ein, basierend auf der Histopathologie und der zellulären Immunität des Patienten, welches immer noch aktuell und für die klinische Einteilung der Patienten wichtig ist [12]. Es besteht aus fünf Säulen, die sich auf zwei Pole und deren Mitte verteilen.

An einem Pol befindet sich die tuberkuloide Lepra (TT) mit einer starken zellvermittelten Immunantwort des Wirtes, bei der keine oder nur ganz selten säurefeste Stäbchen in den Maculae nachweisbar sind und sie somit zur paucibazillären Form (PB) zugeteilt wird. Klinisch weist sie wenige asymmetrisch auf den Körper verteilte hypopigmentierte Hautläsionen mit Hypästhesie und Analgesie sowie mit Trockenheit, Anhidrose und oft Haarlosigkeit (sogenannte Lepraflecken) auf. Die Patienten leiden unter Neuritis mit Schmerzen und motorischen Ausfällen an den am häufigsten befallenen peripheren Nerven *N. ulnaris, N. tibialis posterior* und *N. fibularis* [13].

Am anderen Pol steht die lepromatöse Lepra (LL), bei dem der Wirt keine spezifische immunologische Resistenz gegen das Lepraantigen entwickelt, wodurch sich das *M. leprae* unkontrolliert im Körper vermehren kann [13]. Zahlreiche säurefeste Stäbchen lassen sich in histologischen Präparaten von den Maculae nachweisen. Die LL wird der multibazillären Form (MB) zugeteilt. Nach einem ersten symptomlosen Stadium mit diffuser Rötung der Gesichtshaut (vor allem nach Sonnenexposition) und symmetrisch disseminierten Maculae ohne Hypopigmentierung oder Sensibilitätsverlust treten viele kleine Maculae mit glatter Oberfläche und undeutlichen Abgrenzungen auf. Im späteren Stadium, der makulösen Lepra finden sich *Erythema nodosum* und *Madarosis* (Ausfall der Wimpern und lateralen Augenbrauen) mit geringem Sensibilitätsverlust in den infizierten Hautbereichen. Das fortgeschrittene Stadium ist durch Hautinduration und Hautknötchen, vor allem im Gesicht und an den Ohren gekennzeichnet, welches sich als „Löwengesicht“ (*facies leonina*) darstellt [13]. Bei einem systemischen Befall werden vor allem Nieren und Nebennieren, Milz, Leber, Knochenmark und Hoden infiziert.

Die meisten Lepraerkrankungen gehören zur intermediären Borderline-Gruppe, die sich zwischen den beiden Polen befindet. Die Patienten dieser Lepraform sind immunologisch instabil [14]. Man teilt sie in eine tuberkuloide borderline Lepra (BT), reine borderline Lepra [15] und lepromatöse borderline Lepra (BL) ein. Das klinische Bild der Borderlinegruppe ist sehr divergent und richtet sich je nach Orientierung des Borderlinetyps im Hinblick auf die Pole TT und LL.

Außerhalb dieser Klassifikation steht die indeterminierte Lepra (IL), die zu Beginn der Lepraerkrankung auftritt und meist asymptomatisch ist. Charakteristisch hierfür ist eine einzelne leicht hypopigmentierte und hypästhetische Macula. Sie kann spontan heilen oder sich je nach immunologischer Lage in die TT oder LL entwickeln. Eine seltene Lepraform ist die reine neurale Lepra (PNL). Sie lässt sich durch Neuropathien ohne die lepraspezifischen Maculae beschreiben.

Bei allen Lepraformen kann es zu einem okulären Befall in Form von Neuropathien oder direkter Infiltration der Haut oder des Auges selbst kommen, welche bei ca. 5 % der Leprapatienten zu einer Erblindung als Spätfolge führen kann.

Plötzlich auftretende inflammatorische Phasen während des normalen Krankheitsverlaufes oder nach Beendigung der MDT werden als Leprareaktionen bezeichnet und können bei etwa 50% der Leprapatienten beobachtet werden [16]. Sie sind klinische Manifestationen eines Wechsels im immunologischen Gleichgewicht zwischen dem Bakterium *M. leprae* und dem Wirt [17]. Sie treten vermehrt bei BL und LL auf und können in Zusammenhang mit besonderen Umständen, die das Immunsystem beeinflussen, wie andere Infektions-erkrankungen, Anämie, Schwangerschaft, mentaler und/oder physischer Stress, Pubertät und durchgeführte chirurgische Eingriffe, stehen. Sie sind häufig Ursachen für die Entwicklung von Deformitäten und physischen Behinderungen. Sie lassen sich in zwei Typen unterteilen:

Eine Reaktion Typ 1, die auch unter dem Begriff *reversal reaction* (RR) bekannt ist, tritt vor allem in den ersten 6 Monaten der Therapie auf und entspricht einer allergischen Reaktion vom Typ IV nach Coombs und Gell. Es kommt zu Neuritis und zur Entzündung der Maculae.

Eine Reaktion Typ 2, weist das klinische Bild eines *Erythema nodosum leprosum* (ENL) auf. Das ENL ist ein Beispiel für die allergische Reaktion vom Typ III nach Coombs und Gell, welche nur BL- oder LL-Patienten befallen. Es ist ein systemischer entzündlicher Prozess mit klinischen Manifestationen im Rahmen einer akuten inflammatorischen Reaktion [16]. Bei Ulzeration kann die Leprareaktion Typ 2 eine Übertragungsquelle für Lepra sein und sich in all den Körperregionen festsetzen, die von der Lepra befallen sind und zu schwerwiegenden Infektionen dieser Organe führen, z.B. allergische Vaskulitiden, Iridozyklitis, Uveitis, Orchitis, Nephritis und Lymphadenitis.

Patienten mit einer Leprareaktion vom Typ 1 oder Typ 2 müssen sofort behandelt werden, da sich irreversible Nervenschäden und daraus Deformitäten und physische Behinderungen entwickeln können, die nicht kurativ versorgt werden können. Bei beiden Reaktionstypen werden Kortikosteroide angewandt. Bei Rezidiven der ENL oder therapieresistenter ENL werden Clofazimin und unter strengsten Vorgaben Thalidomid (Contergan) eingesetzt [13].

1.2.3 Diagnose

Nach den Richtlinien der WHO [6] gibt es drei diagnostische klinische Untersuchungskriterien, die auf Lepra schließen lassen:

a) Sensibilitätsverlust auf hypopigmentierten oder rötlichen Hautläsionen (sogenannte „Lepraflecken“)

b) Verdickter peripherer Nerv mit Hypästhesie in den zu versorgenden Hautarealen/ Schwäche der innervierten Muskeln oder

c) der positive Nachweis von säurefesten Stäbchen in einer aus einer Hautläsion entnommenen Hautbiopsie

Liegt mindestens eines dieser Kriterien in einem endemischen Gebiet vor, gilt die Lepraerkrankung als diagnostiziert. Heutzutage wird in endemischen Ländern die Lepraerkrankung hauptsächlich klinisch (a, b oder c ohne Hautbiopsie) diagnostiziert. Nach klinischer Diagnosestellung der Lepra hilft die durchgeführte Hautbiopsie, vor allem zwischen der PB und der MB zu unterscheiden.

Die körperliche Untersuchung basiert auf einer gründlichen Inspektion nach Hautauffälligkeiten und Deformitäten. Zudem werden Sehkraft, Sensibilität und Muskelkraft an den Extremitäten und Augen sowie die Beschaffenheit der peripheren Nerven getestet, um den Schweregrad der Behinderung zu definieren. Nach einem von der WHO vereinfachten Schema ist die multibazilläre Lepra durch fünf oder mehr Hautläsionen definiert. Liegen weniger als fünf Hautläsionen vor, entspricht dies der paucibazillären Form.

Andere Diagnoseverfahren, wie z.B. der Lepromintest, die Histologie peripherer Nerven, der Pilocarpintest und ELISA zeigen eine geringere Genauigkeit und befinden sich weiterhin im Forschungsstadium.

1.2.4 Therapie

Seit 1982 wird von der WHO die MDT empfohlen [18]. Bisher wurde ein Unterschied in der Medikamentenkombination bei PB und MB gemacht. Nach den aktuellen Richtlinien der WHO [19] wurde die Therapie vereinfacht. Sowohl für die PB als auch für die MB wird eine Dreierkombination mit Dapson, Rifampicin und

Clofazimin empfohlen. Die Therapiedauer von 6 Monaten für die PB und 12 Monate für die MB bleibt unverändert.

Die Therapie ist ein *directly observed treatment* (DOT). Das bedeutet, dass die Patienten am Tage der Lepradiagnose den ersten Medikamentenblister für die tägliche Einnahme erhalten und unter Aufsicht von *community health workers* oder Krankenschwestern die monatlich einmalige Dosis von Rifampicin und Clofazimin einnehmen. Nach Beendigung der Medikamentenblister (28 Tage) erhalten die Patienten im Gesundheitszentrum den nächsten Medikamentenblister. Falls sie nicht im Gesundheitszentrum erscheinen, werden sie vom *community health worker* aufgesucht. Somit wird Therapieabbrüchen entgegengewirkt und der Krankheitsverlauf der Patienten besser überwacht, um bei Leprareaktionen oder anderen Komplikationen sofort handeln zu können. Die Leprabehandlung ist seit vielen Jahren, ebenso wie die Tuberkulosebehandlung, kostenlos.

Neben der medikamentösen Therapie spielen Physiotherapie und Ergotherapie zur sekundären und tertiären Prävention von Behinderungen eine wichtige Rolle. Zudem ist die Anwendung von Hilfsmitteln bei physischen Behinderungen und Deformitäten wie z. B. Fußheberorthesen bei Fallfüßen oder spezielle Schuheinlagen bei Sensibilitätsverlust wichtig. Rekonstruktive chirurgische Eingriffe werden bei Patienten mit Deformitäten, wie z.B. Krallenhänden sowie chirurgische Neurolysen bei Fibrosierung der Nerven angewandt.

Neben den kurativen und versorgenden Therapiemaßnahmen sind primäre Präventionsmaßnahmen wie präventive Vorsorgeuntersuchungen von Personen, die in engem Kontakt mit Leprapatienten, v.a. der MB – Form, stehen, oder gegebenenfalls auch eine prophylaktische Behandlung mittels einer BCG-Impfung wichtig. Eine Chemoprophylaxe in Form von einer einmaligen Gabe von Rifampicin oder Dapson in Kombination mit der BCG-Impfung wird in den aktuellen Leitlinien der WHO nicht empfohlen, kann aber laut aktueller Studien die Inzidenz von Lepraneuerkrankungen bei Kontaktpersonen reduzieren [20].

1.2.5 Einteilung des Behinderungsgrades nach WHO

Um eine bessere Kontrolle über die Lepraerkrankung und ihre Behandlung zu haben, erfolgte seitens der WHO die Einführung von GD, die anhand von Untersuchungsergebnissen von Augen, Händen und Füßen erhoben werden. Sie

reichen von G0D bis G2D. Die Einteilung in den einzelnen GD stützt sich auf die Ergebnisse aus Sensibilitäts- und Muskeltests sowie auf die sichtbaren physischen Behinderungen.

G0D: kein Sensibilitätsverlust und kein sichtbarer Schaden an Augen, Händen und Füßen

G1D: Verlust der protektiven Sensibilität an Augen, Händen und/oder Füßen, ohne sichtbaren Schaden oder Deformität

G2D: Deformitäten und/oder sichtbarer Schaden an den Augen (Lagopthalmus und/oder Ektropium, Trichiasis, Hornhauttrübung und oder Sehkraft unter 0,1 oder Finger können im Abstand von 6 Metern nicht mehr gezählt werden), sichtbare Schäden an Händen oder Füßen (Ulkus und/oder traumatischen Läsionen, Ulzerationen, Fallhand und/oder -fuß, Krallenhand und/oder -fuß, Gelenkkontrakturen).

Im Vergleich zur Einteilung nach WHO-Richtlinien wird nach brasilianischen Leitlinien eine reduzierte Sensibilität der Kornea zu G1D gezählt.

1.3 Ethikvotum

Die Studie wurde durch das *centro universiatário luterano de Palmas* (lutherisches Universitätszentrum von Palmas [21]) sowie durch die *Universidade federal do Ceará* (UFC - Bundesuniversität von Ceará) in Fortaleza getragen.

Entsprechende Ethikvoten des *centro universiatário luterano de Palmas* mit der Gutachtennummer 28/2009 sowie der *Universidade federal do Ceará* mit der Gutachtennummer 139/09 liegen vor.

1.4 Ziele der Arbeit

Nach Indien ist Brasilien weltweit das zweite und auf dem amerikanischen Kontinent das Land mit der höchsten Anzahl an neu detektierten Lepraerkrankungen. Daher braucht man Studien, die zum einen die aktuelle Datenlage ermitteln, zum anderen Faktoren bestimmen, die mit erhöhtem Risiko der Entwicklung einer Behinderung einhergehen und schließlich auf diese Infektionskrankheit als aktuelles Problem des öffentlichen Gesundheitswesens hinweisen. Die beiden Publikationen dieser Dissertation sind Teil der interdisziplinären Studie Integrahans MAPATOPI, welche als Zielpopulation ein repräsentatives Patientenkollektiv aus einer hochendemischen Region hatte.
Ein Ziel dieser Studien war es, durch unterschiedliche Datenerhebungen (klinische Untersuchung, Interviews, Patientenakten) eine breitgefächerte Informationslage von neu diagnostizierten Leprapatienten im Hinblick auf Lepra-assoziierte physischen Behinderungen [22] und von Patienten, die die MDT unterbrochen oder abgebrochen haben [23], zu erreichen. Informationen zur Krankheit, ihrer Epidemiologie sowie Charakteristik des Patientenkollektivs sollten erlangt werden, um daraus mögliche Schwachstellen und Missstände im lokalen Lepra-Kontrollprogramm zu filtern und dem nationalen Gesundheitsministerium hiermit Anreize und Argumente zur Entwicklung von Lösungen und Strategien zu liefern, die die Kontrolle der Lepra verbessert und die negativen Folgen der Krankheit reduziert. Für die Auswahl der zu untersuchenden Studienteilnehmer wurden alle in SINAN erfassten Fälle im Untersuchungsgebiet ausgewählt. Dadurch entstand in enger Zusammenarbeit mit dem Gesundheitsministerium von Tocantins eine umfangsreiche Untersuchungspopulation.
In beiden Studien wurden primäre Daten erhoben und sekundäre Daten (aus den Patientenakten und aus dem SINAN) genutzt. Hierdurch konnte die Qualität der primären Gesundheitsversorgung in einer sozial schwächer gestellten Region beurteilt werden.
Bei Häfner et al. (2017) [22] wurden die durch Lepra verursachten physischen Behinderungen in den Vordergrund gestellt. Durch eine dermatoneurologische Untersuchung wurde der aktuelle körperliche Zustand der Probanden ermittelt. Da die Studie von August bis Dezember 2009 durchgeführt wurde und Personen in die Studie aufgenommen wurden, die zwischen 2006 und 2008 zum ersten Mal mit Lepra diagnostiziert wurden, hatte die Mehrheit der Population zum Zeitpunkt

der Studienerhebung die MDT bereits abgeschlossen. Somit lagen der Studie sekundäre Daten aus den Patientenakten wie Informationen zu der Klinik, Therapie, GD am Diagnosetag und des aktuellen Therapiestatus unseres Probandenkollektivs vor. Ein wichtiger Grundpfeiler sollte die Beschreibung der Veränderung des Behinderungsgrades vom Diagnosetag bis zum Zeitpunkt der neurologischen Nachuntersuchung, die im Rahmen der Erhebung der Primärdaten durchgeführt wurde, sein. Dadurch gab sich die grundlegende Fragestellung, ob es zu einer Verbesserung bzw. Verschlechterung der GD kam.
Bei Heukelbach et al. (2011) stand der Fokus auf der MDT. Ziel war es bei dieser Studie, die Faktoren, die mit Therapieabbruch assoziiert sind, zu identifizieren.

2 Publizierte Originalarbeiten

2.1 *High occurrence of disabilities caused by leprosy: census from a hyperendemic area Brazil's savannah region;*

Haefner, K., Walther, F., André Chichava, O., Ariza, L., Alencar, C. H., Freitas de Alencar, M., Novaes Ramos Jr., A., Richter, J., Heukelbach, J.; Leprosy Review, Volume 88: 520-532, (2017) [22]

Lepr Rev (2017) **88**, 520–532

High occurrence of disabilities caused by leprosy: census from a hyperendemic area in Brazil's savannah region

KATHRIN HAEFNER*, FRIEDERIKE WALTHER**, OLGA ANDRÉ CHICHAVA***, LIANA ARIZA***, CARLOS HENRIQUE ALENCAR***, MARIA DE JESUS FREITAS DE ALENCAR***, ALBERTO NOVAES RAMOS JR.***, JOACHIM RICHTER**** & JORG HEUKELBACH*****

**School of Medicine, Heinrich-Heine-University, Dusseldorf, Germany*
***School of Medicine, University of Cologne, Germany*
****Department of Community Health, School of Medicine, Federal University of Ceará, Fortaleza, Brazil*
*****Institute of Tropical Medicine and International Health, Charité Universitätsmedizin, Berlin, Germany*
******College of Public Health, Medical and Veterinary Sciences, Division of Tropical Health and Medicine, James Cook University, Townsville, Queensland, Australia*

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Summary

Objectives: To describe leprosy-related disabilities, we performed a census including people affected by leprosy in 78 municipalities of Tocantins state in northern Brazil. The study consisted of a review of patient charts, structured questionnaires, and clinical examinations for disabilities of eyes, hands, and feet (August–December 2009), according to WHO standards.

Results: A total of 910 individuals diagnosed from 2006 to 2008 were included (clinical examination and application of questionnaires), but information from patient charts was not available in all cases, resulting in different denominators. The majority (783/858; 91·3%) had completed multidrug therapy. The most common clinical findings included: enlarged/painful peripheral nerves (412/910, 45·3%), namely of ulnar (207; 22·7%), posterior tibial (196; 21·6%), peroneal (186; 20·5%), and radial cutaneous nerves (166; 18·2%); reduction/loss of sensibility 201/907 (22·2%) and

Correspondence to: Jorg Heukelbach, Departamento de Saúde Comunitária, Faculdade de Medicina, Universidade Federal do Ceará, Rua Professor Costa Mendes 1608, 5. andar, Fortaleza CE 60430-140, Brazil (Tel: +55-85-33668045; Fax: +55-85-33668050; e-mail: heukelbach@web.de)

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reduced motor function (185/906, 20·4%). At diagnosis, 142/629 (22·6%) had Grade 1 disability (G1D), and 28/629 (4·5%) had Grade 2 disability (G2D). At the time of the study, 178/910 (19·6%) presented with G1D, and 84/910 (9·2%) with G2D. Disability grading was significantly higher in males ($P < 0·01$). Subjects with G2D showed claw hands (26; 2·9%), followed by plantar ulcers (23; 2·5%), abrasion/excoriation on the foot (12; 1·3%), claw foot (7; 0·7%), and drop foot (7; 0·7%).

Conclusions: Leprosy-related disabilities were common in a highly endemic area. Prevention and rehabilitation measures, especially after release from treatment, should be intensified by the primary health care system. Policy makers need to be aware of an ongoing demand for leprosy control programmes, even in a world of constantly reducing leprosy detection.

Keywords: leprosy, disabilities, epidemiology, prevention, Brazil

Introduction

Leprosy is one of the most ancient infectious diseases of humanity, but still poses a health threat in many countries, with most cases occurring in India, Brazil and Indonesia (in 2015 worldwide: 210,758, Brazil: 26,395).[1] Despite decreased leprosy incidence during recent years, peripheral neuropathy and physical disabilities caused by *Mycobacterium leprae* continue to be a major problem, as they may persist for many years and even worsen after release from treatment (RFT). The proportion of people with visible deformity and/or severe visual impairment (i.e. WHO Grade 2 disability – G2D) among newly detected leprosy cases increased worldwide in recent years, from 3·7% (2005) to 6·6% (2015), and in Brazil from 5·8% (2005) to 6·6% (2015).[1–3] A similar upward trend of the rate of newly detected cases with G2D (7·2% in 2015) has been observed in Tocantins State in Brazil's North region, where this study was performed.[4]

In the current WHO Global Leprosy Strategy for 2016–2020, the reduction of the rate of newly diagnosed leprosy patients with G2D to less than one per million population is one of the aims.[5] This indicator for late diagnosis can be reduced by improving coverage and access in endemic areas and targeting case detection among high risk groups.

The present study forms part of a multidisciplinary epidemiological investigation called IntegraHans MAPATOPI, performed in a hyperendemic region in North Brazil. We present the results of clinical examinations, review of patient charts, and structured questionnaires, regarding impairments and disabilities in a population from 78 municipalities.

Methods

The Brazilian General Coordination of Leprosy & Diseases in Elimination (*Coordenação Geral de Hanseníase e Doenças em Eliminação* – CGHDE) of the Ministry of Health identified several years ago 10 high risk leprosy clusters, in order to focus and intensify prevention and control measures.[6] The present study is a cross-sectional study performed in the so-called cluster 1, within the realm of the IntegraHans MAPATOPI project, a major project performed in the four Brazilian states Maranhão [MA], Pará [PA], Tocantins [TO] and Piauí [PI].[7–9] MAPATOPI includes studies on the epidemiological, clinical, psychosocial,

and operational determinants of leprosy. Details of this project have been published previously elsewhere.[6,9,10]

STUDY AREA AND POPULATION

Tocantins, the most recent state of the Brazilian Federation (created in 1988), is located in the central savannah region. The state is subdivided into 139 municipalities with a total population of 1·5 million.[4] Tocantins is considered hyperendemic for leprosy (58·08 new cases/100,000 inhabitants, 2015).[4]

The study was performed in a census population of 78 municipalities of northern Tocantins that formed part of the high risk cluster 1.[10,11] The target population included all individuals newly diagnosed with leprosy from 2006–2008, living and notified as leprosy cases in the study area. Leprosy cases were identified through the electronic database of the National Information System for Notifiable Diseases (*Sistema de Informacão de Agravos de Notificação* – SINAN).[11] If during field visits patients were identified in the local records that had not been notified in SINAN, we included them in the study.

We did not include the municipality of Araguaína, which forms part of cluster 1, a major city in the region with about 120,000 inhabitants. Araguaína has a leprosy reference clinic and shows different characteristics, as compared to the other smaller municipalities that share mainly rural characteristics. The results from Araguaína (147 leprosy-affected individuals) have been published elsewhere.[12,13]

We excluded those who moved to municipalities outside the endemic cluster, and subjects with mental disabilities or other pathologies, such as anxiety disorder or alcohol abuse, which may interact with clinical examinations or interviews. Relapsed leprosy cases were also excluded.

STUDY DESIGN, VARIABLES AND DATA COLLECTION

The census included all leprosy patients of the study area matching the inclusion criteria. Data collection included review of patient charts, clinical examinations, and the application of structured questionnaires.

Variables included demographic information (age, sex, municipality of residence), and clinical data (clinical form, operational classification, disability grade at diagnosis, mode of case detection, date of diagnosis, date of release from treatment and date of last appearance at the health center for treatment). WHO disability grading was based on examinations of eyes, hands and feet, ranging from 0–2.[14] In detail, the following criteria based on WHO definitions were used - G0D: no anesthesia and no visible damage to eyes, hands and feet; G1D: loss of protective sensibility of eyes, hands and/or feet, without visible damage or deformities; G2D: deformities and/or visible damage to the eyes (shown by lagophthalmos and/or ectropion, trichiasis, corneal opacity, visual acuity less than 0·1 or difficulty counting fingers at 6 meters), visible damage to hands or feet (shown by ulcerations and/or traumatic injuries, resorption, ulcers, drop hand, claw hand or foot, drop foot, ankle contracture). As usual in Brazil, sensibility of eyes was assessed under field conditions, and G1D included reduced corneal sensation.

In close cooperation with the Tocantins State Health Secretariat and the Municipality Health Secretariats, field visits were coordinated; they took place from August to December 2009. Previous to field visits, the Municipal Health Secretariats were informed about the timeframe when the team would perform data collection.

During field visits, first the patient charts and the local notification records were reviewed regarding clinical variables. Then, community health agents invited study participants to be interviewed and examined at the health care centres. If individuals after several attempts did not present at the health care centres, we performed home visits accompanied by local community health agents, with direct individual approach to avoid stigma. Some of them had not spoken about their leprosy diagnosis with their families or neighbours.

Data were collected using pre-tested structured questionnaires for data collection. Clinical examinations were performed according to WHO and Brazilian MoH standards[15,16] and focused on body regions, which are usually infected by leprosy: nose, eyes, upper and lower extremities. The nose was examined with a lamp for leprosy related-lesions (perforation of the nasal septum, dryness). Visual acuity was tested using Snellen charts. Sensibility and peripheral nerve testing was performed (eyes, hands, feet) and peripheral nerves of upper and lower extremities (ulnar, median, radial cutaneous, peroneal and posterior tibial nerves) were palpated, as described in detail elsewhere.[17]

Corneal sensation was tested with a standard dental floss applied on the lateral lower quadrant of the cornea. The Semmes-Weinstein monofilament kit was used to test the sensitivity of hands and feet - six sensory sites on the palmar surface of the hands (three ulnar and three median nerve-innervated areas) and nine topographic sites of the feet.[16] G1D sensory disability was defined if the 2g filament (i.e. the third of the six monofilaments) was not felt, and/or if there was corneal sensory loss.

We applied a voluntary muscle strength test to verify the function of the peripheral motor nerves, with the categories strong, weak and paralysed for eyelid closure, finger and thumb abduction, fifth finger intrinsic position, wrist extension, extension of the hallux and dorsiflexion of the foot.

To reduce inter-observer variation, all questionnaires and clinical examinations were applied by previously trained field investigators who were constantly supervised during data collection. Extensive pre-tests were performed under supervision.

DATA ENTRY AND ANALYSIS

Data were entered twice using Microsoft Office Access® 7 (for clinical data) and Epi Info Software Version 3.5.1 (Centers for Disease Control and Prevention, Atlanta USA) for data from questionnaires and examinations. They were cross-checked, and entry-related errors were corrected. Then, a unique database including all information sources was created. Similar answers to open-ended questions were grouped and categorised. The data were analysed using StataSE® (Version 9.1 for Windows, StataCorp LP, College Station, USA). Variables are presented as absolute numbers and relative frequencies. We applied Fisher's exact test to estimate the significance of the difference of relative frequencies.

ETHICS

The study was approved by the Ethical Review Boards of the Federal University of Ceará (Fortaleza, Brazil) and of the Lutheran University of Palmas (Tocantins, Brazil). The study and field research were permitted by the State Health Secretariat of Tocantins, by the National Leprosy Control Program, and by the involved municipalities. Informed written consent was obtained from study participants. The interviews took place in separated rooms to protect privacy. If there were any clinical findings that required further diagnosis or treatment,

participants were referred to the professionals of the local health centre for treatment or other examinations.

Results

Of the target population of 1,488 people from 78 municipalities, 910 (61·2%) subjects of 74 municipalities were included in data analysis. Four municipalities had not notified any case; 549 (36·9%) subjects of the other municipalities had moved to another city outside the endemic cluster, were not met even after home visits or were not known at the local health centres. In 13 (0·9%) individuals, clinical examinations or the questionnaires were incomplete, and another four (0·3%) refused clinical examination. In addition, eight people (0·5%) did not give their consent to be included in the study. We excluded another four people (0·3%), who had not understood the instructions.

The majority of study participants (783/858; 91·3%) had completed multidrug therapy. The clinical information at diagnosis (clinical form, operational classification and disability grading) collected from the patient health records was often incomplete, resulting in different denominators: 745 (81·9%) with information on clinical form, 864 (94·9%) with information on operational classification, and only 629 (68·4%) with information on disability grading.

Of the total of 910 participants, 478 (52·5%) were males; the age ranged from 5 to 98 years (mean = 41·9 years; standard deviation: 18·6 years); 217 (23·5%) were illiterates, and 250 (27·5%) were living in rural areas. The majority (785; 91·3%) had been released after MDT at the time of the study. A total of 483 (55·9%) had been classified as paucibacillary (PB), and 381 (44·1%) as multibacillary (MB). The most common clinical form was indeterminate (282; 37·4 %), followed by borderline disease (233; 30·9%), and tuberculoid form (151; 20·0%).

At the moment of diagnosis, 142/629 (22·0%) had been graded with G1D, and 28/629 (4·4%) with G2D (Table 1). The clinical examination within the realm of the study revealed 178/910 (19·6%) of cases with G1D and 84/910 (9·2%) of G2D.

Details of the clinical examination are presented in Table 2.

Table 1. Grade of disability at physical examination during study, and at diagnosis, total number and stratified by gender ($n = 910$, but complete data not available in all cases)

	Total	Male	Female	
	N (%)	N (%)	N (%)	*P*-value
Grade of disability at diagnosis (patients' charts)				
Grade 0	459 (73·0)	222 (68·7)	237 (77·5)	0·02
Grade 1	142 (22·6)	81 (25·1)	61 (19·9)	
Grade 2	28 (4·4)	20 (6·2)	8 (2·6)	
Grade of disability during study (clinical examination)				
Grade 0	648 (71·2)	301 (63·0)	347 (80·3)	<0·01
Grade 1	178 (19·6)	117 (24·5)	61 (14·1)	
Grade 2	84 (9·2)	60 (12·5)	24 (5·6)	

Dark grey: Distribution of females with G0D (diagnosis – time of study).
Light grey: Distribution of males with G0D (diagnosis – time of study).

Table 2. General physical examination of the population during the study, total number and stratified by gender ($n = 910$, but complete data not available in all cases)

	Total	Males	Females	
	N (%)	N (%)	N (%)	*P*-value
Nasal examination				
Symptoms relating to nose				
Yes	81 (8·9)	40 (8·4)	41 (9·5)	0·56
No	829 (91·1)	438 (91·6)	391 (90·5)	
Signs - lesions and dryness				
Yes	54 (5·9)	29 (6·1)	25 (5·8)	0·89
No	856 (94·1)	449 (93·9)	407 (94·2)	
Ocular examination				
Symptoms related to eyes				
Yes	324 (35·6)	162 (33·9)	162 (37·5)	0·27
No	586 (64·4)	316 (66·1)	270 (62·5)	
Signs - corneal sensibility; reduction or loss of sensibility on both eyes*				
Yes	70 (7·7)	46 (9·6)	24 (5·6)	0·03
No	838 (92·3)	431 (90·4)	407 (94·4)	
Reduction of visual acuity (<0·1) or difficulty counting fingers at 6 meters				
Yes	50 (5·5)	31 (6·5)	19 (4·4)	0·39
No	860 (94·5)	447 (93·5)	413 (95·6)	
Lid closure (Facial nerve)				
Weak/paralysed	30 (3·3)	21 (4·4)	9 (2·1)	0·06
Intact	880 (96·7)	457 (95·6)	423 (97·9)	
Ocular findings*				
Yes	208 (22·9)	130 (27·3)	78 (18·1)	<0·01
No	699 (77·1)	347 (72·7)	352 (81·9)	
Examination of the upper extremities - symptoms				
Yes	363 (39·3)	184 (38·5)	179 (41·4)	0·38
No	547 (60·7)	294 (61·5)	253 (58·9)	
Evaluation of strength - reduced or paralysed on both hands*				
Yes	148 (16·3)	94 (19·7)	54 (12·5)	<0·01
No	760 (83·7)	382 (80·3)	378 (87·5)	
Abduction of digit V (Ulnar nerve)*				
Reduced	115 (12·7)	68 (14·3)	47 (10·9)	0·02
Paralysed	19 (2·1)	15 (3·2)	4 (0·9)	
Intense	774 (85·2)	393 (82·5)	381 (88·2)	
Abduction of thumb (Median nerve)*				
Reduced	80 (8·8)	50 (10·5)	30 (6·9)	0·12
Paralysed	6 (0·7)	4 (0·8)	2 (0·5)	
Intense	823 (90·5)	423 (88·7)	400 (92·6)	
Extension of the fist (Radial nerve)*				
Reduced	42 (4·6)	28 (5·9)	14 (3·2)	0·02
Paralysed	4 (0·4)	4 (0·8)	0	
Intense	863 (95·0)	445 (93·3)	418 (96·8)	
Nerve Palpation - painful or tender nerve - upper extremities				
Yes	302 (33·2)	187 (39·1)	115 (26·6)	<0·01
No	608 (66·8)	291 (60·9)	317 (73·4)	
Ulnar nerve				
Yes	207 (22·7)	138 (28·9)	69 (16·0)	< 0·01
No	703 (77·3)	340 (71·1)	363 (84·0)	
Median nerve				
Yes	109 (12·0)	68 (14·2)	41 (9·5)	0·03
No	801 (88·0)	410 (85·8)	391 (90·5)	
Radial nerve				
Yes	166 (18·2)	101 (21·1)	65 (15·1)	0·02
No	744 (81·8)	377 (78·9)	367 (84·9)	

Table 2. *Continued*

	Total	Males	Females	
	N (%)	N (%)	N (%)	*P*-value
Evaluation of sensibility - reduction or loss of sensibility - both hands				
Yes	59 (6·5)	41 (8·6)	18 (4·2)	<0·01
No	851 (93·5)	437 (914)	414 (95·8)	
Ulnar nerve*				
Yes	58 (6·4)	41 (8·6)	17 (3·9)	<0·01
No	852 (93·6)	437 (91·4)	415 (96·1)	
Median nerve				
Yes	40 (4·4)	27 (5·7)	13 (3·0)	0·07
No	870 (95·6)	451 (94·3)	419 (97·0)	
Examination of the feet - symptoms*				
Yes	429 (47·1)	222 (46·4)	207 (47·9)	0·69
No	479 (52·9)	256 (53·6)	225 (52·1)	
Evaluation of strength on both feet*				
Reduced or paralysed	100 (11·0)	59 (12·4)	41 (9·5)	0·17
Intense	808 (89·0)	417 (87·6)	391 (90·5)	
Extension of the digit I (Fibular nerve)*				
Reduced	85 (9·4)	50 (10·5)	35 (8·1)	0·06
Paralysed	8 (0·9)	7 (1·5)	1 (0·2)	
Intense	815 (89·7)	419 (88·0)	396 (91·7)	
Dorsiflexion of the foot (Fibular nerve)*				
Reduced	48 (5·3)	29 (6·1)	19 (4·4)	<0·01
Paralysed	9 (1·0)	9 (1·9)	0	
Intense	852 (93·7)	439 (92·0)	413 (95·6)	
Nerve palpation - painful or tender nerve - lower extremities*				
Yes	281 (30·9)	161 (33·8)	120 (27·8)	0·05
No	627 (69·1)	315 (66·2)	312 (72·2)	
Tibial posterior nerve*				
Yes	196 (21·6)	104 (21·8)	92 (21·3)	0·87
No	712 (78·4)	372 (78·2)	340 (78·7)	
Fibular nerve*				
Yes	186 (20·5)	117 (24·5)	69 (16·0)	<0·01
No	723 (79·5)	360 (75·5)	363 (84·0)	
Evaluation of sensibility - reduction or loss of sensibility on both feet*				
Yes	194 (21·4)	136 (28·6)	58 (13·4)	<0·01
No	714 (78·6)	340 (71·4)	374 (86·6)	
Clinical findings – eyes*				
Yes	208 (22·9)	130 (27·3)	78 (18·1)	<0·01
No	699 (77·1)	347 (72·7)	352 (81·9)	
Upper extremities*				
Yes	160 (17·6)	100 (21·1)	60 (13·9)	<0·01
No	747 (82·4)	375 (78·9)	372 (86·1)	
Lower extremities*				
Yes	233 (25·7)	149 (31·4)	84 (19·4)	<0·01
No	674 (74·3)	326 (68·6)	348 (80·6)	
Clinical findings on upper extremities and/or lower extremities and/or eyes				
Yes	405 (44·5)	246 (51·5)	159 (36·8)	<0·01
No	505 (55·5)	232 (48·5)	273 (63·2)	
Clinical findings on upper and lower extremities and eyes				
Yes	38 (4·2)	28 (5·9)	10 (2·3)	<0·01
No	872 (95·8)	450 (94·1)	422 (97·7)	

*data not available in all cases.

Table 3. Disabilities of hands and feet, as detected at physical examination during study, total number and stratified by gender ($n = 910$, but complete data not available in all cases)

	Total	Males	Females	
	N (%)	N (%)	N (%)	*P*-value
Eyes	63/910 (6·9)	41/437 (8·6)	22/410 (5·1)	0·05
Corneal opacity	23/909 (2·5)	17/460 (3·6)	6/426 (1·4)	0·06
Trichiasis	1/910 (0·1)	1/476 (0·2)	0	1·00
Reduction of visual acuity less than 0·1 or difficulty counting fingers at 6 meters	50/909 (5·5)	31/446 (6·5)	19/413 (4·4)	0·19
Hands	26/910 (2·9)	20/458 (4·2)	6/426 (1·4)	0·02
Claw hand	26/910 (2·9)	0/458 (4·2)	6/426 (1·4)	0·02
Abrasion/excoriation	6/910 (0·7)	6/472 (1·3)	0	0·03
Palmar ulcer	2/910 (0·2)	2/476 (0·4)	0	0·50
Drop hand	3/910 (0·3)	3/475 (0·6)	0	0·25
Feet	35/910 (3·9)	23/455 (4·8)	12/420 (2·8)	0·12
Plantar ulcer	23/910 (2·5)	16/462 (3·5)	7/425 (1·6)	0·14
Abrasion/excoriation	12/910 (1·3)	7/471 (1·5)	5/427 (1·2)	0·78
Claw foot	7/910 (0·8)	2/476 (0·4)	5/427 (1·2)	0·27
Drop foot	7/910 (0·8)	7/471 (1·5)	0	0·02
Eyes, lower and/or upper extremities	110/910 (12·1)	74/404 (15·5)	36/396 (8·3)	$<0·01$
Eyes, lower and upper extremities	2/910 (0·2)	1/477 (0·2)	1/431 (0·2)	1·00
Lower and/or upper extremities	54/910 (5·9)	39/439 (8·2)	15/417 (3·5)	$<0·01$
Lower and upper extremities	7/910 (0·8)	4/474 (0·8)	3/429 (0·7)	1·00

In general, disabilities detected in this study were more common in males, especially regarding visual acuity, plantar and palmar sensibility, muscle strength of the hands and palpation of the nerves of the upper extremities. Disability grading was significantly higher in males ($P < 0·01$; Table 1).

Table 3 details the findings of physical disabilities. Most subjects with G2D showed strongly limited visual acuity ($<0·1$), followed by claw hands, corneal opacity and plantar ulcers. Table 4 details the GD at diagnosis, as compared to the assessment during the study; 18·2% presented with a higher GD than at diagnosis, whereas 15·9% improved. The remaining 65·9% maintained their GD, most of them with G0D.

Figures 1a and 1b depict the distribution of subjects with G1D and G2D, stratified by gender and age, at the time of the study. Both genders presented an increase with higher age.

Discussion

This cross-sectional study shows that more than a quarter of the subjects from a hyperendemic area suffered from leprosy-related impairment and that 10% presented visible disabilities (G2D). Tendered or painful nerves were the most common pathological findings, and related to nerve damage,[18,19] which is an indicator for the development of present and future disabilities.[12] The occurrence of damaged peripheral nerves is linked to increased disability, as recently demonstrated in a Brazilian cohort study.[18] At the time of the study, G2D had increased considerably. As a chronic condition, the sensory and nerve evaluation in leprosy cases should be performed as standard at every examination: at time of diagnosis and at time of every examination after diagnosis as well as examination after RFT.

Table 4. Correlation between grade of disability (GD) at diagnosis (patient charts) and during study (clinical examination)

	GD at diagnosis (patient charts)			
	0*	1	2	Total
GD during study (clinical examination)	N (%)	N (%)	N (%)	N (%)
0*	365 (58·0)	86 (13·7)	6 (0·9)	457 (72·6)
1	71 (11·3)	36 (5·7)	8 (1·3)	115 (18·3)
2	23 (3·7)	20 (3·2)	14 (2·2)	57 (9·1)
Total	459 (73·0)	142 (22·6)	28 (4·4)	629 (100)

Light grey: Improvement of GD (diagnosis – time of study).
Dark grey: Worsening of GD (diagnosis – time of study).
To read cross tabulation: at diagnosis 459 (73·0%) patients had no impairments; at clinical examination during study, 365 (58%) were still G0D, 71 (11,3%) became G1D and 23 (3·7%) G2D.

The ulnar nerve is usually the most commonly affected peripheral nerve, followed by the tibial nerve.[20,21] In some studies most of the impairments were seen on the feet, followed by the hands and eyes.[12,22] Independent of the topographic location, prevention measures including self-care activities have to be applied during the entire lifetime to prevent further disabilities.[20]

By intensification of the Brazilian Leprosy Control Program, a continuing reduction of newly detected cases of leprosy has been achieved. These efforts should necessarily be integrated with programs for rehabilitation and prevention of disabilities. Patients with disabilities need long-term special treatment, physiotherapy and instruction in self-care awareness, so that a reintegration in the social and working life is possible. The accessibility to local rehabilitation centres must be guaranteed for every leprosy patient in any stage of the disease. According to official instructions of the Brazilian Ministry of Health and of the State Health Secretariat of Tocantins, every municipality is supposed to provide a specific room for physiotherapy.[23]

The long-term development of disabilities is reflected by the grade of disability (GD) at diagnosis and later moments in time. In both examinations, 365 (58·0%) subjects presented Grade 0 disability (G0D). However, the frequency of current G2D (9·1%) worsened

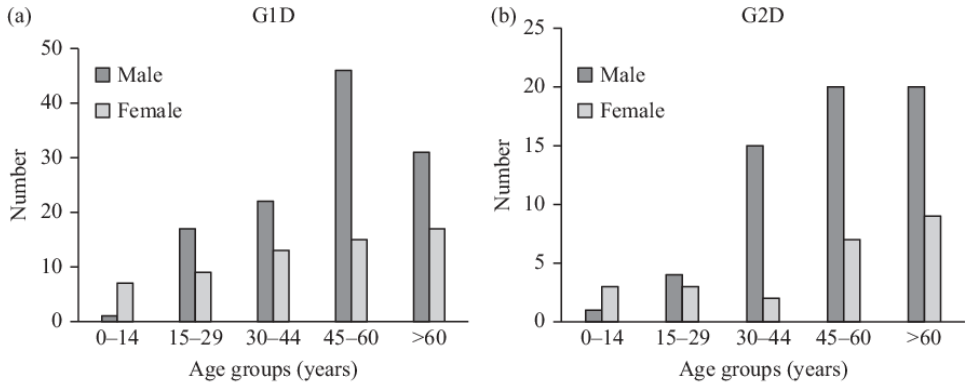

Figure 1a/b. Absolute frequency of the subjects with G1D and G2D, stratified by gender and age group, at the time of the study.

considerably in comparison to G2D at diagnosis (4·4%). The distribution of individuals with G1D showed a higher level in the current evaluation. This shows that the impairments worsened during/after RFT and that secondary prevention measures need to be intensified. In previous studies, a similar trend has been observed.[12,24,25] In an Indonesian study, up to 5 years after RFT there was an increase from 31·0% at diagnosis to 49·0% of patients with G2D.[22] After RFT, the patients are usually out of the monitoring of the health services and not followed up, but during this period leprosy-related sequelae mostly occur. Signs and symptoms often cannot be interpreted correctly by the patients, resulting in delayed diagnosis and treatment, and finally to developing of impairments. The follow-up of patients after RFT has to be systematically integrated into the health services to ensure disease and morbidity management, to instruct in awareness of the disease, and to respond immediately and accordingly if leprosy related sequelae appear.[12,26] Considering the chronic nature of leprosy, these activities should continue, even when the incidence is decreasing. A recent study shows considerable leprosy mortality in Brazil, despite the existence of a preventable and cost-effective treatment. The authors emphasised that sustainable control measures should include appropriate management and systematic monitoring of leprosy-related complications, such as severe leprosy reactions and adverse effects to multidrug therapy.[27] Early diagnosis, the completion of MDT and adequate treatment of leprosy-related reactions prevent the development of disabilities, so that the already existing programmes have to be intensified with focus on these aspects.[25] Furthermore, management, prevention, and socioeconomic rehabilitation should be intensified to further prevent disabilities after RFT.[12,22] Stigma-related aspects should be considered to integrate people affected by leprosy-related disabilities into the workplace and society.[22,28,29]

An additional finding in our study was the predominance of male subjects with pathological results in the clinical examination. This observation coincides with other studies from Brazil and elsewhere.[22,24,29–32] Late diagnosis causes the occurrence of advanced disease, including MB classification or already existing G1D or G2D. Reasons for delayed diagnosis are multiple and may include fear of loss of social and economic life; e.g. loss of work, as demonstrated in an Indian study.[33] In general, late diagnosis is usually more common in males, and the female population shows a more distinct health-seeking behaviour as compared to males.[12,29,31] Due to cultural and socioeconomic factors, Latin American men are considered as the provider, the 'stronger' gender and invulnerable. In rural areas, reduced geographic access to the health system may also be related to delayed diagnosis. Males also often fail to attend consultations because of conflict with working hours. Therefore, several Brazilian Health Care Programs extended the opening times (weekends and at night) of local healthcare centres, with activities focused on the male population.[32,34]

The physical hard work, which in our study setting traditionally is more common in males, comprises a higher risk for developing traumas and lesions especially after RFT, increasing the risk of secondary disabilities in leprosy-affected individuals.[35] In addition, males have been shown to be less aware of disease-specific risks for disabilities.[29] For example, not wearing adequate shoes in case of loss of plantar sensibility may lead to plantar ulcers[36,37] or not interpreting leprosy-related symptoms correctly.[38] A Brazilian study about factors associated with delay in diagnosis revealed that nearly half of the participants did not take their symptoms seriously.[38] Independent of gender, it is important to intensify health education measures to increase the awareness of the disease and to help interpreting leprosy-related symptoms correctly.[38]

In our study, advanced age was associated with higher risk of disabilities, independent of gender. Similar results could be found in other studies.[19,39] Relating to the chronic features of leprosy, the risk of developing disabilities increases with duration of disease, and thus with age.[12,19]

Decentralisation of leprosy control programmes are known to improve case detection and to reduce the number of treatment defaulters. In Brazil, the constant integration of leprosy control into primary health care for several years, based on local municipal healthcare units, supports the relationship and confidence between the health professionals and the patients.[40] The local healthcare centres are important for the day-to-day management relating to diagnosis and treatment, improving early detection of the disease, of reactive episodes and of leprosy-related sequelae. Decentralisation of the health system has also been recommended by WHO.[41]

Limitations

Incompleteness of secondary SINAN and patients' health record data, mainly concerning clinical variables at diagnosis (clinical form, operational classification and GD at diagnosis), may have caused bias; the distributions of GD and gender at diagnosis and at the moment of investigation are based on different population sizes and thus should be interpreted with care. Professionals have to be trained in handling the information health systems and to manage, report and process data collection.[42]

In this study, we focused on clinical examination of the upper and lower extremities, because the interpretation of evaluation of the eyesight is limited, especially in difficult field conditions[43,44]

Inter-observer variation may have occurred, especially regarding the clinical examination. We aimed to minimise this error by applying intensive training and supervision by experienced researchers and clinicians during data collection.

Conclusions

This study performed in a highly endemic area in Brazil shows that the presence of leprosy-related disabilities after RFT is still common. Intensive longitudinal follow-up after RFT has to be integrated systematically into the local health services to prevent the occurrence and progression of disabilities. The access to management, prevention and rehabilitation of the disabilities has to be intensified and guaranteed for every person affected by leprosy. Difficult-to-reach-groups, e.g. working males and rural populations with difficult access to the health system, have to be integrated more intensively into the focus of primary health care. As the first contact people for the patient, professionals from local healthcare units must be permanently trained in detecting leprosy and their sequelae and in transferring the data correctly to the patients' charts and datasets.

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Author contributions

Conceived and designed the study: ANRJ, JH, MFA, CHA, LA, KH, FW, OAC; Preparation of study and field supervision: MFA, JH, LA, ANRJ, CHA; Data collection, entry and management: KH, FW, OAC, LA; Analysis and interpretation of results: KH, JH, MFA, CHA, ANRJ, JR; Wrote first draft of paper: KH, JH; Performed input to paper and approved final version: all authors.

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2.2 *Interruption and Defaulting of Multidrug Therapy against Leprosy: Population-Based Study in Brazil's Savannah Region;*

Heukelbach, J., André Chichava, O., Rodrigues de Oliveira, A., Häfner, K., Walther, F., Morais de Alencar, C.H., Novaes Ramos Jr., A., Cavalcante Ferreira, A., Ariza, L., PLoS Neglected Tropical Diseases, Volume 5: e1031, (2011) [23]

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PLoS NEGLECTED TROPICAL DISEASES

Interruption and Defaulting of Multidrug Therapy against Leprosy: Population-Based Study in Brazil's Savannah Region

Jorg Heukelbach[1,2]*, Olga André Chichava[1], Alexcian Rodrigues de Oliveira[1], Kathrin Häfner[3], Friederike Walther[4], Carlos Henrique Morais de Alencar[1], Alberto Novaes Ramos Jr.[1], Adriana Cavalcante Ferreira[5], Liana Ariza[1]

1 Department of Community Health, School of Medicine, Federal University of Ceará, Fortaleza, Brazil, **2** Anton Breinl Centre for Public Health and Tropical Medicine, School of Public Health, Tropical Medicine and Rehabilitation Sciences, James Cook University, Townsville, Australia, **3** School of Medicine, University of Düsseldorf, Düsseldorf, Germany, **4** School of Medicine, University of Cologne, Cologne, Germany, **5** State Leprosy Control Program, State Health Secretariat of Tocantins, Palmas, Brazil

Abstract

Background: Low adherence to multidrug therapy against leprosy (MDT) is still an important obstacle of disease control, and may lead to remaining sources of infection, incomplete cure, irreversible complications, and multidrug resistance.

Methodology/Principal Finding: We performed a population-based study in 78 municipalities in Tocantins State, central Brazil, and applied structured questionnaires on leprosy-affected individuals. We used two outcomes for assessment of risk factors: defaulting (not presenting to health care center for supervised treatment for >12 months); and interruption of MDT. In total, 28/936 (3.0%) patients defaulted, and 147/806 (18.2%) interrupted MDT. Defaulting was significantly associated with: low number of rooms per household (OR = 3.43; 0.98–9.69; p = 0.03); moving to another residence after diagnosis (OR = 2.90; 0.95–5.28; p = 0.04); and low family income (OR = 2.42; 1.02–5.63: p = 0.04). Interruption of treatment was associated with: low number of rooms per household (OR = 1.95; 0.98–3.70; p = 0.04); difficulty in swallowing MDT drugs (OR = 1.66; 1.03–2.63; p = 0.02); temporal non-availability of MDT at the health center (OR = 1.67; 1.11–2.46; p = 0.01); and moving to another residence (OR = 1.58; 95% confidence interval: 1.03–2.40; p = 0.03). Logistic regression identified temporal non-availability of MDT as an independent risk factor for treatment interruption (adjusted OR = 1.56; 1.05–2.33; p = 0.03), and residence size as a protective factor (adjusted OR = 0.89 per additional number of rooms; 0.80–0.99; p = 0.03). Residence size was also independently associated with defaulting (adjusted OR = 0.67; 0.52–0.88; p = 0.003).

Conclusions: Defaulting and interruption of MDT are associated with some poverty-related variables such as family income, household size, and migration. Intermittent problems of drug supply need to be resolved, mainly on the municipality level. MDT producers should consider oral drug formulations that may be more easily accepted by patients. Thus, an integrated approach is needed for further improving control, focusing on vulnerable population groups and the local health system.

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* E-mail: heukelbach@web.de

Introduction

Leprosy control is based on early diagnosis, treatment, and cure, aiming at the elimination of sources of infection and of sequels in affected individuals. Similar to other countries, in Brazil leprosy control measures are integrated into general public health care, thus facilitating access to affected individuals and reduction of disease-related stigma [1].

Interruption and defaulting of multidrug therapy against leprosy (MDT) are still important obstacles of disease control in many endemic countries, with consequences for both patients and the control programs: low adherence is responsible for potentially remaining sources of infection, incomplete cure, and irreversible complications, and in addition may lead to multidrug resistance [2]. In Brazil, the number of patients defaulting treatment was reduced from 3,148 individuals in 2002 to 529 in 2009 (with approximately 49,000 and 37,500 new cases, respectively) [3].

The causes leading to low adherence and non-compliance to MDT are diverse and may include socio-economical, cultural, psychosocial, behavioral, drug-related and disease-related factors, as well as health service-related aspects [2,4–9]. For

Author Summary

Leprosy is still a public health problem in Brazil, and low adherence to multidrug therapy against leprosy (MDT) is an important obstacle of disease control. This may lead to remaining sources of infection, incomplete cure, complications, and multidrug resistance. We performed a study in 78 municipalities in central Brazil, and interviewed leprosy-affected individuals. In total, 3% of patients defaulted, and 18.2% interrupted MDT. Risk factors for interruption of treatment include: reduced number of rooms per household (OR = 1.95; p = 0.04); difficulty in swallowing MDT drugs (OR = 1.66; p = 0.02); temporal non-availability of MDT drugs at health center (OR = 1.67; p = 0.01); and moving residence after diagnosis (OR = 1.58; p = 0.03). Defaulting MDT was significantly associated with: reduced number of rooms per household (OR = 3.43; p = 0.03); moving to another residence (OR = 2.90; p = 0.04); and low family income (OR = 2.42; p = 0.04). Our study shows that defaulting and interruption of MDT against leprosy are associated with some poverty-related variables such as family income, household size, and migration. Intermittent problems of drug supply need to be resolved, mainly on the municipality level. MDT producers should consider drug formulations that are more easily accepted by patients. An integrated approach is needed for further improving control, focusing on most vulnerable population groups and the local health system.

example, a recent study from India identified stigma as the most common reason given by defaulters, but failed to detail data and to compare these factors with non-defaulters [4]. In Paraíba State in the northeast of Brazil, defaulting of MDT was associated with regular alcohol use, but not with clinical characteristics [5]. However, that study involved only 13 patients who defaulted, as compared to 28 patients finishing treatment regularly. Here we present - as part of a major epidemiological investigation in 78 municipalities in Brazil - population-based data to further investigate factors associated with interruption and defaulting of MDT in a hyperendemic area.

Methods

Study area and population

Tocantins State is located in the central savannah region of Brazil (Figure 1). The state has been created in 1988 and has a total population of 1,3 million (2009), distributed throughout 139 municipalities; 83% of the municipalities have less than 10,000 inhabitants. Tocantins is hyperendemic for leprosy: in 2009, a total of 1,345 new cases were notified, and the detection rate was 88.54/100.000 inhabitants.

The present study is part of a major epidemiological investigation performed in 79 municipalities of northern Tocantins. These municipalities are at highest risk for leprosy transmission, according to a recent cluster analysis performed by the Brazilian Ministry of Health (Figure 1) [10,11]. The target population included all individuals newly diagnosed with leprosy from 2006–2008, living and notified as leprosy cases in these municipalities. We excluded the municipality of Araguaína from the present analysis, the biggest city in the region with about 120 thousand inhabitants. Araguaína has a leprosy reference clinic and shows different characteristics, as compared to the other smaller

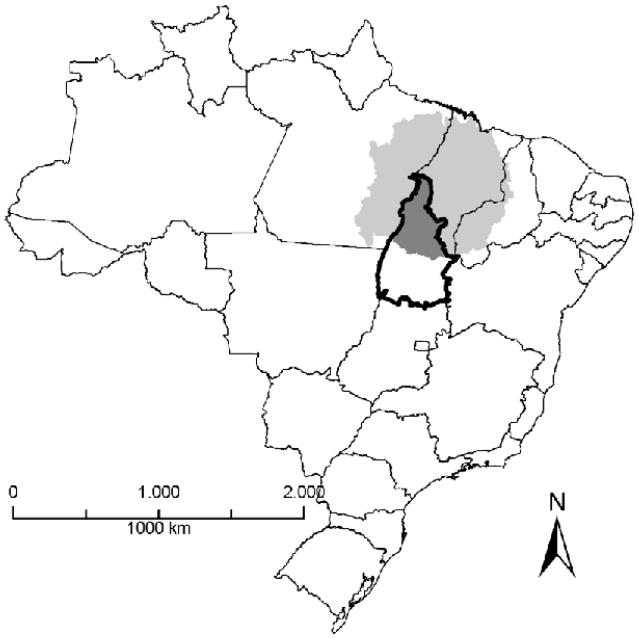

Figure 1. Study area (dark gray area) in Tocantins State, Brazil. The light gray area indicates the cluster of high transmission risk situated in the states Maranhão, Pará, Tocantins and Piauí.
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municipalities that share mainly rural characteristics. These results will be published elsewhere.

We also excluded patients who moved to municipalities outside the endemic cluster, suffered from mental disability or who have shown other characteristics that impeded an interview, such as individuals under the influence of alcohol. Relapsed leprosy cases were also excluded. Individuals who had died after diagnosis were not included in data analysis.

Study design and data collection

The 78 Municipal Health Secretariats were informed by the Tocantins' State Health Secretariat about the study and the timeframe when the team would perform field visits for data collection. Previous to field visits, the target population was identified in the database of the National Information System for Notifiable Diseases (*Sistema de Informação de Agravos de Notificação* – SINAN). In the municipalities, the patients' charts and the local notification records were first reviewed regarding clinical variables (clinical form, operational classification, disability grade at diagnosis, mode of case detection, date of diagnosis, date of release from treatment and date of last appearance at health center for treatment). If in the local records patients were identified that had not been notified, we included them in the target population. Then, affected individuals were invited by community health agents to be interviewed at the local health care center. If individuals did not present at the health care center, we performed home visits accompanied by local community health agents. Data were obtained at this occasion according to a previously defined framework, using pre-tested structured questionnaires. The framework comprised of four blocks of independent variables possibly associated with the outcomes: 1. Socio-demographic block (gender, age, marital status, education, residence area, number of rooms, number of persons per household, household income, migration); 2. Disease-related block (clinical form of disease, operational classification, disability grade, leprosy reaction, adverse events to MDT, difficulty swallowing MDT drug); 3. Health service-related block (mode of case detection, non-availability of MDT drugs, distance to health care center, perceived difficult access to health care center); 4. Knowledge, attitudes and practices block (alcohol consumption, information of peer persons regarding disease, knowledge on leprosy and cure). Data were collected from September to December 2009.

To reduce inter-observer bias, all questionnaires where applied by two previously trained field investigators (OAC, ARO) who were supervised during the entire study. Data from patients' charts were collected by another two investigators (KH, FW). Extensive pre-tests were performed under supervision.

Data entry and analysis

Data were entered twice, using Epi Info software version 3.5.1 (Centers for Disease Control and Prevention, Atlanta, USA) and cross-checked for entry-related errors. Answers to open-ended questions were grouped according to similarities and categorized for bivariate analysis. Open-ended questions included information on clinical characteristics for definition of leprosy reaction and adverse events; and questions on knowledge, attitudes and practices. Data analysis was done using STATA version 9 (Stata Corporation, College Station, USA).

As the number of individuals defaulting MDT was relatively low, two separate bivariate analyses were performed, with two different outcomes based on the non-attendance of patients at treatment centers:

1. Defaulting from treatment:

   For this outcome, we used the definition of the Brazilian Ministry of Health [12]: defaulters were defined as individuals that did not complete MDT and who did not present to the health care center for the monthly supervised treatment for at least 12 months. We reviewed the most recently available SINAN database of 2009 regarding this information and in addition collected information on defaulting from the local patients' charts.
2. Interruption of treatment:

   Interruption of MDT was defined as duration of treatment $\geq$7 months in the case of the paucibacillary form of disease (PB) or $\geq$13 months in the case of the multibacillary form (MB). Standard MDTs as set by the World Health Organization (and adopted by the Brazilian Ministry of Health) are 6 four-week blister packs for PB, and 12 four-week blister packs for MB patients. Data analysis of interruption included only individuals that had potential time to complete the treatment (all PB cases; MB cases that had begun treatment $\geq$13 months previous to data collection).

Variables were first analyzed and presented in a bivariate manner. Odds ratios and their respective 95% confidence intervals are given. We applied Fisher's exact test to estimate significance of the difference of relative frequencies. Continuous and discrete variables were not normally distributed and thus compared applying the Wilcoxon rank sum test for unmatched data.

Unconditional logistic regression analysis using backward elimination was then performed to calculate adjusted odds ratios for the independent association between 1) interruption of; and 2) defaulting MDT, and the respective explanatory variables. Results of both analyses are presented separately. In addition to sex, age and leprosy form (PB/MB) which we used as adjusting variables throughout multivariate analysis, variables with a p value<0.25 in the Fisher's exact test were entered into the initial regression models, and then backward elimination was run. To remain in the model, a significance of $p<0.05$ was required. Variables were checked for collinearity. Confounding and interaction between variables were also investigated by stratification and by constructing 2×2 tables. All variables that remained in the final models are presented, and odds ratios were adjusted for all other variables in the respective model.

Ethics

The study was approved by the Ethical Review Board of the Federal University of Ceará (Fortaleza, Brazil) and by the Ethical Review Board of Lutheran University of Palmas (Tocantins, Brazil). Permission to perform the study was also obtained by the Tocantins State Health Secretariat, the State Leprosy Control Program and the municipalities involved.

Informed written consent was obtained from all study participants after explaining the objectives of the study. In the case of minors, consent was obtained from a caretaker. Interviews were always performed separately to guarantee strict privacy, and the diagnosis of leprosy was not given to family members or other community members, in case the patient had not revealed the diagnosis. If any leprosy-associated pathology was observed during the interview or during clinical examination (data of clinical examination to be published elsewhere), participants were referenced to the responsible health care service.

Results

Study population and basic characteristics

Of the target population of 1635 individuals from 78 municipalities, 936 (57.2%) from 74 municipalities were included in data analysis; one municipality did not diagnose a single case of leprosy in the study period, and another three municipalities had few cases, but no participants were included (non-consent or not encountered). Twelve patients refused to participate in the study. We excluded another 13 (five under of influence of alcohol that impeded an interview; four convicted; three severely sick who were hospitalized; and one due to advanced age). In addition, 674 were not encountered even after home visits, were not known at the local health centers, or had moved to another city outside the cluster. For the analysis of interruption of MDT 130 individuals were excluded (92 did not have information about date of the beginning of treatment or last date of supervised monthly dose in the health care center, and 38 were classified as MB leprosy with treatment started <13 months before data collection). Thus, data analysis regarding defaulting included 936, and regarding interruption 806 individuals. Information from patients' charts was available in 894 of cases.

Of the total of 936 individuals, 491 (52.5%) were males; the age ranged from 5 to 98 years (mean = 42.1 years; standard deviation: 18.8 years). Two-hundred and twenty-five (24.0%) were illiterate. Median monthly family income was R$ 465 (about 270 USD at the time of the study; interquartile range: R$ 300–R$ 900). In total, 497 (55.6%) were classified as PB leprosy, and 395 (44.1%) as MB.

We identified 28 (3.0%) patients who defaulted MDT; 16 defaulters were included by reviewing the SINAN data information system, and an additional 12 locally in the patients' charts. Only 5 individuals were in the both databases. In total, 147/806 (18.2%) interrupted MDT.

Factors associated with interruption of MDT

Factors associated with interruption of MDT are detailed in Table 1. Moving to another residence after diagnosis and living in a small residence were significantly associated with interruption. In addition, disease- and health service-related variables (difficulty in swallowing MDT drug; temporal non-availability of MDT drugs) were significantly associated with an increased chance of interruption of treatment (Table 1). Interestingly, disease-related factors such as the clinical form, presence of leprosy reactions or occurrence of adverse events to MDT did not play a significant role.

Figure 2 depicts the frequency of interruption of MDT, stratified by age groups and gender. In general, the 16–30 year-olds showed the highest chance of interruption, as compared to all other age groups together (OR = 1.84; 95% confidence interval: 1.20–2.77; p = 0.04). This effect could be mainly attributed to the 16–30 year-old males, who showed the highest frequency of interruption (34.4%), roughly a two-fold difference to females of the same age group (17.6%; p = 0.01; Figure 2).

Logistic regression analysis identified temporal non-availability of MDT drugs at the health care center as an independent risk factor for treatment interruption (Table 2). An increased number of rooms per household (as an indicator for wealth) was identified as an independent protective factor.

Factors associated with defaulting MDT

Bivariate analysis of factors associated with defaulting MDT is depicted in Table 1. Several socio-economic variables (number of rooms per household; moving to another residence after diagnosis; family income) were significantly associated with defaulting (Table 1). Similar to interruption of MDT, disease-related factors did not play a significant role. Health service variables did also not show any significant association.

In logistic regression analysis, we identified the number of rooms per residence as a factor independently associated with defaulting, with a protective odds ratio of 0.67 for each additional room in the household (Table 2), but no other factors.

Discussion

Low adherence to drugs is in general a major obstacle in the control of infectious diseases that require prolonged treatment, such as leprosy and tuberculosis. Our comprehensive population-based study shows that poverty, behavior, drug-related and service-related factors were associated with adherence to MDT, hampering leprosy control in a hyperendemic area in Brazil, and suggest evidence-based actions for improving control measures.

It is widely believed that understanding and behavior of patients in relation to drug compliance are largely influenced by their socio-economic condition and level of knowledge; socio-economic factors were previously suggested to influence adherence to MDT [5,7,13]. Even though family income as a direct indicator of poverty was not significantly associated with low adherence (but with defaulting), number of rooms was identified as an independent risk factor in both bivariate and multivariable analyses. Poverty and its consequences, similar to other neglected tropical diseases, has been shown to be associated with leprosy in general [14], and our results reflect this complex interaction of causation leading to higher risk of disease in underprivileged populations.

In addition, population movements are usually associated with socio-economic conditions in Brazil. In our study, people who had moved to another residence were more vulnerable for low adherence. These people may lose their bonds with community health workers and other health professionals of the primary health care centers, besides other factors that change in life when moving to another place. Similar findings have been made in India and southeast Brazil, where treatment interruption due to migration has been reported [15,16]. In the case of tuberculosis, moving to another district with subsequent change of health unit was also shown to increase the risk of defaulting treatment in Uganda [17]. On the other hand, changing residence due to leprosy was clearly not a factor that played a role in our study (data not shown).

Interestingly, the frequency of defaulting MDT was relatively low, as compared to other settings [2,4,13,18,19], with a rate of only 3%. In Tocantins, the defaulting rate was 47% in 2005, but was reduced drastically in subsequent years [20]. This may reflect the success of efforts made in the last years by Tocantins's health services. In fact, the Brazilian national and state leprosy control programs have put a major effort in improving the decentralized primary health care services, with 90% population coverage of the Family Health Program in Tocantins. As another consequence, variables related to health services seemed to play a minor role for defaulting in our study, despite the identification of temporary shortage of drugs as a significant risk factor for interruption of MDT. We have shown previously that the patients of this area answered most commonly to an open-ended question about the reason for interrupting MDT with temporary shortage of drugs at the health care center, but median time of interruption was only 15 days which indicates that this operational issue was usually resolved quickly [21]. In fact, these logistical problems occurred mainly on the municipality level, as MDT provided by the State

Table 1. Bivariate analysis of factors associated with interruption of, and defaulting multidrug therapy against leprosy.

Variables	Interruption of MDT (n = 806)*				Defaulting MDT (n = 936)*			
	Examined n	Positive n (%)	OR (95% CI)	*P* value	Examined n	Positive n (%)	OR (95% CI)	*P* value
Socio-demographic								
Gender								
Male	429	88 (20.1)	1.39 (0.95–2.03)	0.08	491	14 (2.9)	0.90 (0.39–2.07)	0.85
Female	377	59 (15.7)	Reference		445	14 (3.2)	Reference	
Age group (years)								
0–15	67	9 (13.4)	0.70 (0.28–1.60)	0.46	77	3 (3.9)	1.20 (0.19–4.99)	0.60
16–30	181	47 (26.0)	1.59 (0.95–2.67)	0.07	207	7 (3.4)	1.00 (0.30–3.22)	1.00
31–45	205	37 (18.1)	Reference		237	8 (3.4)	Reference	
46–60	200	32 (16.0)	0.86 (0.50–1.50)	0.60	234	8 (3.4)	1.01 (0.33–3.16)	1.00
≥61	153	22 (14.4)	0.76 (0.41–1.40)	0.39	181	2 (1.1)	0.32 (0.03–1.63)	0.20
Marital status								
Single	222	34 (15.3)	0.73 (0.46–1.14)	0.17	256	12 (4.7)	2.20 (0.89–5.43)	0.07
Married	479	95 (19.8)	Reference		549	12 (2.2)	Reference	
Divorced	52	10 (19.2)	0.96 (0.42–2.04)	1.00	63	2 (3.2)	1.47 (0.16–6.82)	0.65
Widowed	52	8 (15.4)	0.73 (0.29–1.65)	0.58	67	2 (3.0)	1.38 (0.15–6.39)	0.66
Education								
Never attended school	191	35 (18.3)	1.00 (0.63–1.55)	1.00	225	6 (2.7)	0.85 (0.28–2.21)	0.83
Attended school at any time	612	112 (18.3)	Reference		707	22 (3.1)	Reference	
Residence area								
Rural	219	45 (20.6)	1.24 (0.82–1.86)	0.30	252	9 (3.6)	1.30 (0.51–3.05)	0.52
Urban	586	101 (17.2)	Reference		683	19 (2.8)	Reference	
Number of rooms per residence								
1–2	55	16 (29.1)	1.95 (0.98–3.70)	0.04	59	5 (8.5)	3.43 (0.98–9.69)	0.03
≥3	749	130 (17.4)	Reference		874	23 (2.6)	Reference	
Number of persons/household								
1–2	25	148 (16.9)	0.90 (0.54–1.47)	0.72	176	9 (5.1)	2.10 (0.82–4.96)	0.08
≥3	657	121 (18.4)	Reference		759	19 (2.5)	Reference	
Household income/month†								
<R$ 465	199	34 (17.1)	0.92 (0.57–1.43)	0.75	232	12 (5.1)	2.42 (1.02–5.63)	0.04
≥R$ 465	545	100 (18.4)	Reference		681	15 (2.2)	Reference	
Moved to another residence after diagnosis								
Yes	179	43 (24.0)	1.58 (1.03–2.40)	0.03	210	11 (5.2)	2.9 (0.95–5.28)	0.04
No	624	104 (16.7)	Reference		722	17 (2.4)	Reference	
Disease-related								
Clinical form								
Tuberculoid	148	25 (16.9)	0.91 (0.52–1.60)	0.8	156	9 (5.8)	1.03 (0.29–3.74)	0.6
Boderline	197	38 (19.3)	1.08 (0.65–1.76)	0.8	239	7 (2.9)	3.00 (0.92–10.3)	0.05
Lepromatous	83	14 (16.9)	1.12 (0.54–2.20)	0.9	91	1 (1.1)	0.53 (0.01–4.43)	1.0
Indeterminate	277	50 (18.1)	Reference		290	6 (2.1)	Reference	
Operational classification								
Multibacillary	331	67 (20.2)	1.27 (0.87–1.84)	0.23	496	17 (3.4)	0.74 (0.30–1.72)	0.56
Paucibacillary	473	79 (16.7)	Reference		393	10 (2.5)	Reference	
Disability grade at diagnosis (DG)								
DG II	26	7 (26.9)	1.48 (0.51–3.83)	0.44	–	–	–	–
DG I	134	14 (10.5)	0.47 (0.24–0.87)	0.01	146	4 (10.5)	0.86 (0.20–2.74)	1.00
DG 0	422	84 (19.9)	Reference		471	15 (19.9)	Reference	
Difficulty swallowing MDT drug								

Table 1. Cont.

Variables	Interruption of MDT (n = 806)*				Defaulting MDT (n = 936)*			
	Examined n	Positive n (%)	OR (95% CI)	*P* value	Examined n	Positive n (%)	OR (95% CI)	*P* value
Yes	130	33 (25.4)	1.66 (1.03–2.63)	0.02	153	3 (2.0)	0.60 (0.11–2.01)	0.60
No	671	114 (17.0)	Reference		778	25 (3.2)	Reference	
Type I or II leprosy reaction during treatment (as reported by patient)								
Yes	61	15 (24.6)	1.51 (0.76–2.86)	0.22	75	3 (4.0)	1.39 (026–4.73)	0.49
No	745	132 (17.7)	Reference		861	25 (2.9)	Reference	
Adverse events to MDT (as reported by patient)								
Yes	389	73 (18.8)	1.07 (0.74–1.56)		461	13 (2.8)	0.89 (0.39–2.03)	0.85
No	417	74 (17.8)	Reference	0.72	475	15 (2.9)	Reference	
Health service-related								
Mode of case detection at primary health care center								
Spontaneous demand	555	101 (18.2)	Reference		603	20 (3.3)	Reference	
Contact examination	35	5 (14.3)	0.75 (0.22–2.02)	0.66	47	2 (4.3)	1.30 (0.14–5.62)	0.67
Case detection campaign	15	5 (33.3)	2.25 (0.59–7.38)	0.17	157	1 (0.6)	0.19 (0.00–1.19)	0.01
Referred from other center	145	27 (18.6)	1.03 (0.62–1.67)	0.90	18	1 (5.6)	1.71 (0.04–12.07)	0.47
Other	10	1 (10)	0.50 (0.01–3.68)	1.00	10	1 (10)	3.24 (0.70–25.38)	0.30
Temporal non-availability of MDT drug at health care center								
Yes	228	55 (24.1)	1.67 (1.11–2.46)	0.01	265	9 (1.5)	1.19 (0.47–2.82)	0.67
No	573	92 (16.1)	Reference		666	19 (2.9)	Reference	
Distance to health care center								
>30 minutes	154	29 (18.3)	1.04 (0.64–1.65)	0.91	186	5 (2.7)	0.90 (0.26–2.45)	1.00
≤30 minutes	634	116 (18.8)	Reference		731	22 (3.0)	Reference	
Perceived difficult access to health care center								
Yes	172	35 (20.4)	1.18 (0.75–1.84)	0.44	201	3 (1.5)	0.42 (0.81–1.41)	0.17
No	620	110 (17.7)	Reference		721	25 (3.5)	Reference	
Knowledge and attitudes								
Continued drinking alcohol during treatment								
Yes	52	14 (26.9)	1.72 (0.83–3.35)	0.10	64	3 (4.7)	0.61 (0.17–3.25)	0.44
No/Never drunk	742	131 (17.7)	Reference		858	25 (2.9)	Reference	
Told household members about leprosy diagnosis								
Yes	778	146 (18.8)	Reference	0.01	907	27 (3.0)	Reference	
No	25	0 (0)	0 (0–0.67)		26	1 (3.9)	1.30 (0.31–8.6)	0.55
Knew leprosy before diagnosis								
Yes	697	121 (17.4)	Reference		808	23 (2.9)	Reference	
No	105	26 (24.8)	1.57 (0.92–2.59)	0.08	124	5 (4.0)	1.43 (0.42–3.96)	0.40
Knew someone with leprosy before diagnosis								
Yes	518	86 (16.6)	Reference		610	16 (2.6)	Reference	
No	282	61 (21.6)	1.39 (0.94–2.03)	0.09	319	12 (4.0)	1.45 (0.62–3.31)	0.41
Thinks that leprosy is curable								
Yes	728	127 (29.0)	Reference		847	25 (3.0)	Reference	
No	38	11 (17.5)	1.92 (0.84–4.14)	0.08	46	3 (6.5)	2.29 (0.43–7.97)	0.17
Does not know	37	8 (21.6)	1.31 (0.50–3.01)	0.51	–	–	–	–

*Information not available in all cases.
†At the time of the survey 1US$ was equivalent to 1.72R$, and R$ 465,- the official minimum wage as set by the Federal Government.
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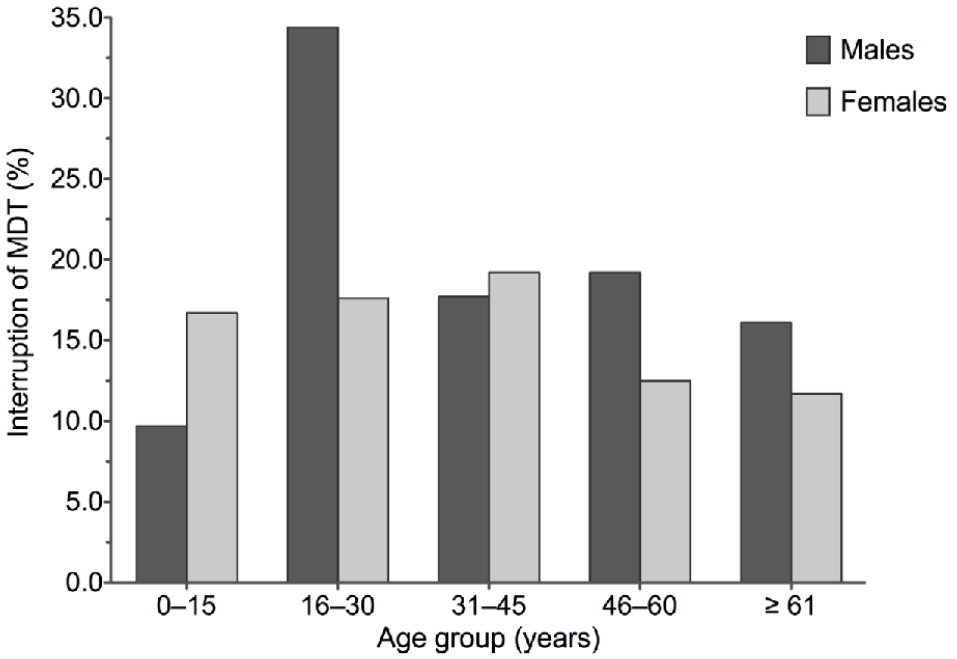

Figure 2. Relative frequency of interruption of MDT, stratified by gender and age group.
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Leprosy Control Program to the municipalities did not suffer any shortage in the study period (A.C.F., unpublished observation). In other countries and settings, where leprosy control programs are not yet well established, such as in northern Mozambique, Nigeria and Sudan, health-service related factors play a more crucial role [4,7,18,19,22].

Our data also indicate that in a setting with an established leprosy control program, clinical variables are of minor importance for low adherence to MDT. In case of leprosy reactions, for example, the primary health care services and the reference centers seem to be prepared to cope with the situation. Similarly, previous studies from northeast Brazil, the Philippines and Nepal suggested that clinical data such as type of leprosy, occurrence of reactions or disability grading at diagnosis would not play a significant role in the given context [2,5,23]. Difficulty in swallowing drugs was previously suggested as a factor associated with low adherence to MDT [2]. Considering also the long course of treatment, this shows the need for the search of new formulations that may be better accepted by patients.

Studies from other parts of the world, mainly from the South Asian and Southeast Asian sub-regions, identified other risk factors for low adherence. For example, in the Philippines adverse events were given by the patients as the most important reason (40%) for defaulting [2]. People in Assam (India) who defaulted treatment mentioned loss of occupational hours when going to the health care center (33,1%), adverse events (26,0%) and social stigma

Table 2. Multivariate logistic regression analysis of factors associated with interruption of, and defaulting multidrug therapy against leprosy, adjusted by sex, age and disease classification.

Variables	Interruption of MDT		Defaulting MDT	
	Adjusted OR (95% CI)	*P* value	Adjusted OR (95% CI)	*P* value
Temporal non-availability of drugs at health care center	1.56 (1.05–2.33)	0.03	–	–
Each additional room per residence	0.89 (0.80–0.99)	0.03	0.67 (0.52–0.88)	0.003
Male sex	1.35 (0.93–1.97)	0.12	0.79 (0.36–1.72)	0.55
Age group 16–30 years	0.99 (0.98–1.00)	0.13	1.05 (0.43–2.56)	0.91
Multibacillary disease	1.12 (0.76–1.66)	0.56	0.70 (0.31–1.56)	0.38

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(18,1%) as the most common reasons [13]. About 10 years ago, these factors were identified in a qualitative study from Espírito Santo State in Brazil [16]. Since then, Brazilian control programs have improved considerably, e.g. by performing health education on adverse events and leprosy reactions, by training health care professionals and by improved access of the users to the primary health care system. The results of our study reflect these efforts and highlight the differing situation in other countries.

Available evidence on the influence of demographic variables on adherence to treatment is contradictory. Similar to the study from the Philippines [2], demographic data such as gender, age and civil status were not associated with low adherence in our study population. In contrast, in endemic regions of Nepal and India, more males than females completed treatment, and illiteracy was also significantly associated with low treatment compliance [9,13]. However, both studies had some methodological problems, and analysis of data is limited. Interestingly, our study showed highest interruption rates in young males, when data were stratified by gender. This indicates that factors are multifaceted and that in this case, young males, who are generally known to show insufficient health care behavior, should be considered a vulnerable group for low adherence. In fact, the Brazilian Ministry of Health has taken into consideration the special needs of the male population and recently launched an integrative program focusing on male gender issues [24].

Similar to leprosy, tuberculosis needs prolonged treatment and has also shown to reveal problems regarding adherence. Improving adherence to treatment against leprosy can thus be expected to have positive impact also on other diseases, such as tuberculosis. In fact, the factors associated with low adherence to tuberculosis are similar. For example, in Ethiopia, the occurrence of adverse events to tuberculosis treatment was found to be a significant risk factor for defaulting, whereas knowledge about duration of treatment was protective and increased the odds of terminating treatment [25]. A study from Nepal identified distance to health care services and low knowledge on disease and its treatment as risk factors for non-adherence to tuberculosis directly observed short-course (DOTS) [26].

An ancillary finding was the detection of incomplete patients' charts and registries in many cases. We detected in total 128 leprosy cases that were not included in the national SINAN database for notifiable diseases, and a considerable number of cases of abandonment from treatment, which had not been registered as such in SINAN. In addition, only in 72.1% (645/894) information on degree of disability at diagnosis was available in the patients' charts. The quality of patients' records and datasets has improved in the past years, but there is still a clear need for more complete data sets and patient charts, as suggested recently in a study performed in northeast Brazil [27].

Though being a population-based study performed in a considerable number of municipalities in a leprosy hyperendemic region, our study is subject to limitations. First, the number of defaulters, as a result of the ongoing leprosy control measures, has been reduced significantly in the past years, and we included only 28 patients who defaulted treatment. This hampered statistical analysis to some degree. Second, non-participation bias, mainly of those who abandoned treatment, may have played a role. Thus, we performed an additional analysis using a less stringent criterion for compliance: interruption of treatment, based on the duration of treatment. However, this analysis did not take into account adherence to drugs taken at home, but was based on appearance at the health care centers for the monthly supervised dose, which should be taken into account in the interpretation of results. Finally, incomplete patients' charts and subsequent missing data hampered analysis regarding clinical variables in some cases. On the other hand, integration of local primary health care professionals and of the State and Municipal Leprosy Control Programs reduced non-participation bias.

We conclude that in an area in Brazil where leprosy control actions are well established, adherence to MDT is a result of a complex interaction between different socio-cultural, service-related, drug-related and economical factors. Intermittent problems of drug supply need to be resolved, mainly on the municipality level. MDT producers should consider oral drug formulations that may be more easily accepted by patients. An integrated approach is needed to further improve adherence and other aspects of leprosy control, such as early diagnosis, including the stakeholders involved: patients and their families, health care professionals, and policy makers [6,28,29]. Improved adherence to MDT will further improve the leprosy control programs and in addition minimize the risk of possibly upcoming drug resistance.

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Author Contributions

Conceived and designed the experiments: JH LA CHMA ANR ACF. Performed the experiments: LA CHMA OAC ARO KH FW. Analyzed the data: JH LA OAC. Wrote the paper: JH LA CHMA ANR ACF.

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3 Diskussion

3.1 Vorkommen von Behinderungen in einem endemischen Gebiet

Im Rahmen der körperlichen Untersuchung konnten die meisten pathologischen Ergebnisse bei der Palpation der peripheren Nerven festgestellt werden. Vergrößerte und/oder schmerzhafte Nerven korrelieren mit einer Nervenschädigung und sind ein wichtiger Indikator für aktuell oder zukünftig auftretende Behinderungen [24]. Am stärksten waren bei der Untersuchung der *N. ulnaris*, gefolgt vom *N. tibialis posterior* befallen, was national und international bereits beschrieben wurde [13, 25]. Eine regelmäßige standardmäßige Untersuchung der Nerven und der Sensibilität sollte vor, während und nach der MDT durchgeführt werden. Da eine Neuritis stumm verlaufen kann oder Symptome der Neuropathien von den Patienten oft nicht richtig gedeutet werden, hilft die dermatoneurologische Untersuchung mit Palpation der Nerven bei der Diagnosestellung und der nachfolgenden Therapie.

Zum Zeitpunkt der Studie hatten 91,3% (783/858) der Studienteilnehmer die MDT bereits beendet und wurden somit als austherapiert eingestuft. Die Anzahl an Probanden mit G2D hatte sich in der körperlichen Untersuchung im Vergleich zu der Evaluation am Diagnosetag (von 4,4 auf 9,1%) verdoppelt. In nationalen und internationalen Studien konnte ebenfalls dieser negative Trend nach Beendigung der MDT gesehen werden [26-28]. In einer brasilianischen Studie aus Rio de Janeiro zeigten 40% der Patienten mit MB-Form eine Verschlechterung ihrer physischen Behinderungen 10 Jahre nach erfolgreicher Beendigung der MDT [28]. In der Studie wurden der initiale GD und die Anzahl an Lepraläsionen bei Diagnosestellung sowie das Vorhandensein von Neuritis als Kriterien gesehen, die mit der Verschlechterung des Behinderungsgrads einhergingen. In einer indischen Studie wuchs der prozentuale Anteil an G2D-Patienten von 31% auf 49% fünf Jahre nach Beendigung der MDT [29].

Grundsätzlich werden eine späte Diagnosestellung, ein fortgeschrittener Schweregrad der Erkrankung sowie das Vorhandensein von Neuritis als Ursachen der Verschlechterung bzw. der Entwicklung von physischen Behinderungen angesehen [28, 30]. Als eine weitere Ursache wird häufig das Fehlen der

medizinischen Nachsorge nach erfolgreicher Beendigung der MDT angegeben [30]. Die monatlichen Vorstellungen der Leprapatienten in den *local health care centres* zur Therapieüberwachung und die dementsprechenden regelmäßigen medizinischen Untersuchungen werden nach erfolgreichem Abschluss der MDT nicht mehr durchgeführt. Eine Nachuntersuchung ist bei beschwerdefreien Patienten nicht Routine. Die Patienten fallen daher aus dem Gesundheitssystem mit regelmäßigen medizinischen Kontrollen heraus. Eine erneute klinische Untersuchung erfolgt erst, wenn sich die Patienten mit neu aufgetretenen Symptomen oder Leprareaktionen vorstellen, häufig, wenn die körperlichen Schäden bereits irreversibel sind. Da die Patienten diese Symptome, vor allem Neuropathien, oft nicht richtig deuten, verzögert sich der sofortige und adäquate Therapiebeginn. Die Entstehung oder Verschlechterung von physischen Behinderungen und somit die Verschlechterung des GDs sind die Folge. Leprareaktionen oder Spätkomplikationen der MDT können noch Jahre bis Jahrzehnte nach Beendigung der MDT auftreten [13, 26, 30, 31]. Die Lepraerkrankung und ihre Folgen enden nicht mit Abschluss der MDT, sondern müssen ähnlich chronischer Erkrankungen regelmäßig medizinisch überwacht werden. In den „*Global Leprosy Strategy 2016-2020. Accelerating towards a leprosy-free world*“ der WHO [7] wird gefordert, die bereits mit MDT behandelten Leprapatienten auf Entstehung von physischen Behinderungen zu überwachen. Dies impliziert eine bessere medizinische Kontrolle mit regelmäßiger dermatoneurologischer Untersuchung der Patienten auch nach Abschluss der MDT. Somit können neu aufgetretene physische Beeinträchtigungen oder auch Komplikationen wie Leprareaktionen/MDT-Versagen frühzeitig erkannt und rechtzeitig behandelt werden [24, 32]. Schulungen des Gesundheitspersonals und der Patienten zur Erkennung von Lepra-assoziierten Symptomen und zum eigenen Körperbewusstsein sowie Präventionsmaßnahmen sollten sich nicht nur auf die Zeit der MDT beschränken, sondern sollten nach erfolgreicher Beendigung der MDT fortgeführt werden [26, 29].

Im Rahmen der Datenerhebung für die Studie konnten mehrere Fälle ausfindig gemacht werden, die die Bedeutung der regelmäßigen medizinischen Überwachung nach Beendigung der MDT verstärken. So konnten neu aufgetretene unbehandelte Ulcera, Neuritiden und sogar Leprareaktionen durch die dermatoneurologische Untersuchung bei einigen Studienteilnehmern

diagnostiziert werden. Bei einem Studienteilnehmer konnte eine bisher unbehandelte ENL festgestellt werden. Bisher nicht bekannte Ulcera wurden entdeckt. Mit Hilfe der *local health care centres* wurden diese direkt behandelt oder an Kliniken, die auf die Lepraerkrankung spezialisiert sind, überwiesen. Andererseits gab es auch positive Fälle, bei denen Probanden mit speziellen Hilfsmitteln wie z. B. einer Fußheberorthese bei Fallfüßen oder speziellen Schuheinlagen bei plantaren Ulcera versorgt waren.

Durch die Etablierung des Leprakontrollprogramms in die primäre Gesundheitsversorgung konnte die Anzahl der Lepraneuerkrankungen in den letzten Jahren in Brasilien deutlich gesenkt werden. Diese Anstrengungen müssen für die Einführung einer regelmäßigen medizinischen Kontrolle der bereits behandelten Patienten investiert werden. In einer brasilianischen Studie konnte erst kürzlich gezeigt werden, dass Lepra auch letale Verläufe hat, obwohl eine effektive Therapie mit der MDT existiert [33]. In der Studie wurden Kontrollmaßnahmen empfohlen, die ein adäquates Kontrollmanagement und ein systematisches Monitoring von Lepra-assoziierten Komplikationen, wie schwere Lepra-Reaktionen oder adverse Reaktionen durch die MDT, einschließen. Andere Studien schlossen sich der Forderung nach regelmäßiger medizinischer Überwachung der bereits behandelten Leprapatienten mit systematischer Integration in das Gesundheitswesen an [26, 34].

Patienten mit bereits bestehenden physischen Behinderungen haben wie chronisch kranke Patienten den Anspruch auf eine spezifische Langzeitbehandlung. Die Bereitstellung von Hilfsmitteln sowie eine regelmäßige Physiotherapie sind die Voraussetzungen für eine Reintegration in das soziale Leben und Arbeitsleben. Vom Brasilianischen Gesundheitsministerium sowie im Falle der vorliegenden Studie vom Gesundheitsministerium Tocantins wird gefordert, dass jeder Bezirk einen Raum im *primary health care centre* zur Verfügung stellt, der alleinig für die Physiotherapie benutzt wird [21]. Das Recht auf eine zeitlich unbegrenzte medizinische Kontrolle sowie Therapie und Nachsorge (z. B. Physiotherapie) sollte im nationalen, aber auch im internationalen Lepra-Kontrollprogramm fest verankert sein und dementsprechend medizinisch ausgebildetes Personal sowie finanzielle Unterstützung zur Verfügung gestellt werden.

Die Voraussetzung für die Vermeidung von physischen Behinderungen ist die frühe Diagnosestellung, die Vervollständigung der MDT und die schnelle und richtige Behandlung von Lepra-assoziierten Reaktionen [28]. Eine frühe Diagnosestellung wird oft dadurch erschwert, dass die Patienten die Symptome der Lepraerkrankung oder ihrer Spätkomplikationen nicht richtig deuten. Ihnen fehlt häufig das entsprechende Wissen und das adäquate Gesundheitsbewusstsein. Durch Aufklärungskampagnen/Workshops/Vorträge kann das Gespür der Patienten für die Erkrankung und ihre Symptome geweckt werden. Neu aufgetretene Symptome/Komplikationen können besser erkannt werden und somit schneller behandelt werden, was für das weitere klinische Outcome maßgebend ist.

Durch die systematische Untersuchung von Personen, die in näherem Kontakt (Familienangehörige, enge Freunde) zu neu diagnostizierten Leprapatienten stehen, erhofft man sich, bisher nicht diagnostizierte Lepraerkrankungen früh zu detektieren. Zum Beispiel im Rahmen einer subklinischen Infektion, bei der die Lepra-assoziierten Symptome nicht besonders stark ausgeprägt sind, die Patienten aber unbewusst eine Infektionsquelle darstellen. Gemäß den Richtlinien der WHO „*Global Leprosy Strategy 2016-2020. Accelerating towards a leprosy-free world*“ [7] wurde die Untersuchung von Kontaktpersonen in das nationale Lepra-Kontrollprogramm Brasiliens integriert.

Durch die Verbesserung des Leprakontrollprogramms, vor allem durch ihre Integration in die primäre Gesundheitsversorgung, konnte zwar die Anzahl der Lepraneuerkrankungen in Brasilien gesenkt werden, dennoch ist der prozentuale Anteil an Patienten mit G2D unter den Neuerkrankungen gestiegen. Daraus lässt sich auf eine verspätete Diagnosestellung der Lepraerkrankung schließen. Bereits bei Diagnosestellung besteht oft die schwerere MB-Form mit bereits vorhandenen physischen Behinderungen. Hierfür gibt es multiple Ursachen wie mangelnde Aufklärung, schlechter Zugang zu der primären Gesundheitsversorgung, schlecht ausgebildetes medizinisches Fachpersonal, Angst vor sozialer Isolation (Verlust der Arbeit, Stigmatisierung) sowie auch die deutlich häufigere Betroffenheit von männlichen Patienten unter den neu diagnostizierten Leprapatienten mit G2D. In der Bevölkerung besteht weiterhin der Bedarf in der Aufklärung von Lepra als heilbare Infektionskrankheit und ihrer Symptome sowie in der Schulung von medizinischem Fachpersonal.

Männer, vor allem in der Altersgruppe 45-60 Jahre, waren von physischen Behinderungen deutlich häufiger betroffen. Dies lässt sich in nationalen und internationalen Studien bestätigen [26, 27, 29, 35-37]. Männer besitzen im Vergleich zu Frauen eine schlechtere Körperwahrnehmung und ein mangelndes Gefühl für pathologische physische Veränderungen, so dass Lepra-assoziierte Symptome von ihnen oft nicht richtig eingeschätzt werden können. Dies führt dazu, dass sie die lokalen *health care centres* erst dann aufsuchen, wenn die Symptome ausgeprägt sind und subjektiv als sehr einschränkend wahrgenommen werden. Bei Diagnosestellung besteht oft ein fortgeschrittener Erkrankungsstatus mit der MB-Form und teilweise mit bereits bestehenden physischen Beeinträchtigungen/Behinderungen (G1D/G2D). Aufgrund der späten Diagnosestellung kommt es zu einem späten Therapiebeginn und hierdurch zu möglichen chronischen Beeinträchtigungen.

In mehreren Studien konnte aufgezeigt werden, dass Männer wegen der ihnen zugeschriebenen Rolle des „stärkeren Geschlechts“ gerade in sozial schwächer gestellten Ländern/Regionen seltener und vor allem meist zu spät zum Arzt gehen [26, 35, 36]. Sie haben Angst, sozial und ökonomisch isoliert zu werden – zum Beispiel ein potenzieller Arbeitsplatzverlust, wenn sie ihre Arbeitszeiten nicht einhalten können, um einen Arzt aufzusuchen. Damit die Arbeitszeiten einem Besuch im *health care centre* nicht im Wege stehen, wurden die Öffnungszeiten dieser vielerorts in Brasilien entsprechend verlängert [26, 38].

Des Weiteren sind Männer oft einem größeren Risiko ausgesetzt, sich im Rahmen physischer Arbeit Verletzungen/Läsionen zuzuziehen. Besonders nach Beendigung der MDT kann dies zu sekundären Behinderungen führen. Im Vergleich zu dem weiblichen Geschlecht ist das Gesundheitsbewusstsein sowie die Durchführung von Sekundär- bzw. Tertiärprävention der Männer nicht stark ausgeprägt. Zum Beispiel wird oft das Tragen von geschlossenen Schuhen zur Vermeidung von Ulcera vergessen. Das brasilianische Gesundheitsministerium hat sich deshalb dieser Situation angenommen und entsprechende integrative Programme, bei denen speziell auf das männliche Geschlecht eingegangen wird, initiiert [38, 39]. Die WHO hat ebenfalls die Problematik der besonderen Betroffenheit der Männer erkannt und legte in den aktuellen „*Global Leprosy Strategy* 2016-2020“ die Früherkennung der Lepraerkrankung, vor allem in Risiko- und Randgruppen wie z. B. arbeitenden Männer und Kindern, als eines der

wichtigsten Ziele fest [7]. Dadurch soll die Entwicklung der Lepra-assoziierten physischen Behinderungen als Konsequenz der Späterkennung und dem folgenden späten Therapiebeginn verhindert werden.

3.2 Faktoren, die mit einem Therapieabbruch assoziiert sind

Die zweite Publikation dieser Dissertation von Heukelbach et al. (2011) konzentrierte sich auf die Studienpopulation von Patienten, die die MDT abgebrochen oder unregelmäßig eingenommen haben.

Vor allem bei Infektionskrankheiten ist die regelmäßige Medikamenteneinnahme in der Kontrolle und Eindämmung der Transmission sehr wichtig. Es zeigte sich, dass die Nichteinnahme oder unregelmäßige Einnahme der MDT mit den sozioökonomischen Konditionen und dem Wissensstand der Patienten korrelierte [40-42]. Das Familieneinkommen war jedoch mit der unregelmäßigen Einnahme nicht signifikant assoziiert, jedoch mit der Nichteinnahme der MDT. Die Agglomeration von Menschen (Anzahl der Räume pro Familie) als Indikator für Armut spielte in der bivariaten und multivariaten Analyse als ein unabhängiger Risikofaktor eine Rolle. Die Studie bekräftigte die bereits bekannte Assoziation von Armut und dem erhöhten Risiko der Entstehung von vernachlässigten Tropenkrankheiten, zu denen die Lepraerkrankung gezählt wird [43].

Im Gegensatz zu Brasilien spielen klinische Faktoren wie unerwünschte Therapienebenwirkungen der MDT oder Leprareaktionen in Südostasien und Südasien eine wichtige Rolle [44]. In Indien sind mögliche fehlende Arbeitsstunden, die im Rahmen der DOT entstünden, ungünstige Therapieverläufe und die soziale Stigmatisierung Gründe für das Abbrechen der MDT [41]. In einer philippinischen Studie nannten 40% der Leprapatienten die unerwünschten Therapienebenwirkungen als Ursache für den Therapieabbruch [44]. Die zuletzt genannten Faktoren deckten sich mit den Ergebnissen einer vor 10 Jahren durchgeführten brasilianischen Studie aus dem Bundesstaat Espirito Santo [45]. Maßnahmen wie vermehrte Schulungen des medizinischen Fachpersonals, Aufklärungen über unerwünschte Therapienebenwirkungen, lepraassoziierte Komplikationen wie Reaktionen/MDT-Versagen sowie ein besserer Zugang der Bevölkerung zu der primären Gesundheitsversorgung führten zu einer

Verbesserung des Leprakontrollprogrammes und somit zu einer Reduktion der Anzahl der Therapieabbrecher/-unterbrecher. Die vorliegende Studie unterstreicht diesen Erfolg. 2005 lag die Therapie-Abbruchsrate bei 47% in Tocantins [23]. In dieser Studie konnte lediglich bei 3% der Studienteilnehmer ein Therapieabbruch festgestellt werden. In anderen Studien zeigten sich vergleichsweise höhere Therapie-Abbruchsraten [46-48].

Die MDT charakterisiert sich durch eine lange Dauer (6 bis 12 Monate) sowie die tägliche Einnahme von mehreren großen Tabletten. Die Schwierigkeit, diese Tabletten einzunehmen, ist gelegentlich ein Faktor für die geringe Einhaltung der MDT [44]. Daher wird eine Überholung der MDT mit kürzerer Therapiedauer sowie einer geringeren Anzahl an Tabletten gefordert.

Aufgrund der hohen Arbeitslosenquote und der dadurch verbundenen Suche nach neuen Arbeitsmöglichkeiten gehört die Migration in der ärmlich ruralen Bevölkerung zur Normalität. Leprapatienten, die ständig ihren Wohnort wechseln, sind gefährdeter, die MDT zu unterbrechen oder gar abzubrechen. Durch ihren Umzug geht die Bindung zu dem medizinischen Personal der *local health care centres* verloren, und sie fallen zunächst aus dem Raster des Leprakontrollprogramms. Im Hinblick auf die korrekte Durchführung der MDT stellt dies ein großes Problem dar, wie sich in Studien aus Indien oder Südbrasilien zeigte [45, 49]. In der vorliegenden Studie konnte nicht festgestellt werden, dass Patienten wegen der Lepraerkrankung aufgrund sozialer Ausgrenzung oder bestehender Stigmatisierung umgezogen sind. Vielmehr war meistens die schlechte Arbeitssituation der Auslöser für den Umzug.

Im Hinblick auf andere Infektionskrankheiten wie z. B. die Tuberkulose ist die regelrechte Einnahme der antituberkulösen Therapie - wie die MDT bei der Lepraerkrankung - für die Heilung sowie für die Eindämmung der Transmission wichtig. In einer Studie aus Uganda konnte gezeigt werden, dass Umzüge ein erhöhtes Risiko für die Unterbrechung oder gar den Abbruch der Therapie bedeuten [50]. Daraus lässt sich erkennen, dass sich die Bestrebungen des brasilianischen Gesundheitsministeriums und die deutlich verbesserte Integration des Leprakontrollprogramms in die primäre Gesundheitsversorgung ausgezahlt haben. Durch diese Dezentralisierung wurde der Zugang zur primären Gesundheitsversorgung für die Patienten und die regelmäßige Kontrolle durch

medizinisches Fachpersonal deutlich verbessert. Dies führte zu einer besseren Beziehung und zu einem besseren Vertrauen zwischen medizinischem Personal und den Leprapatienten. Es kommt zu einer besseren Kontrolle der regelmäßigen Medikamenteneinnahme. Dadurch konnte die Compliance der Patienten bzgl. MDT gestärkt werden, was zur beträchtlichen Reduktion des Anteils an Therapieabbrechern oder -unterbrechern führte.

Faktoren bezüglich der Gesundheitsversorgung spielten in der Studie eine unbedeutende Rolle für einen Therapieabbruch. Das Fehlen der MDT in den *local health care centres* konnte als signifikanter Risikofaktor für die Unterbrechung der MDT identifiziert werden. Im Durchschnitt lag die Unterbrechung der MDT bei 5 Tagen, was eine schnelle Lösung des Medikamentenengpasses erkennen lässt. In anderen Ländern, in denen das Lepra-Kontrollprogramm noch nicht in der primären Gesundheitsversorgung integriert ist, spielten Faktoren, die das Gesundheitswesen betreffen, dagegen eine bedeutende Rolle wie z. B. in Mosambik, Nigeria und im Sudan [40, 47, 48]. Da das Leprakontrollprogramm im Gegensatz zu Brasilien nicht fest in der primären Gesundheitsversorgung verwurzelt ist, kann die von der WHO geforderte bessere medizinische Kontrolle und Unterstützung der Patienten kaum gewährleistet werden.

Wie bereits bei Häfner et al. (2017) konnte eine männliche Dominanz in dem Patientenanteil gesehen werden, der die MDT unterbrochen oder abgebrochen hat. Bei den Therapieabbrechern bzw. -unterbrechern betraf es vor allem die jungen Männer zwischen 16 und 30 Jahren. Junge Männer gehören überwiegend der arbeitenden Bevölkerung an und müssen die Familie durch ihr Einkommen ernähren. Wie bereits in 3.1. beschrieben versucht Brasilien durch Verlängerung der Öffnungszeiten einer vermeintlichen Nichteinnahme der DOT aufgrund der Arbeitszeiten entgegenzuwirken.

3.3 Limitationen der Studien

Im Rahmen der Feldarbeit wurde die dermatoneurologische Untersuchung nicht immer von derselben, sondern von mehreren Personen durchgeführt, was zu einem systematischen Fehler führen könnte. Zur Reduktion dieses Untersucherbias wurde die überwiegende Anzahl der klinischen Untersuchungen

von zwei Personen (FW und KH) durchgeführt. Beide Untersucherinnen wurden vor Beginn der Studie von einer brasilianischen Krankenschwester, einer Spezialistin für Lepraerkrankung, in der dermatoneurologischen Untersuchung intensiv geschult und mehrfach vor und während der Studie auf Kohärenz der Untersuchungen kontrolliert. Dadurch sollten unterschiedliche Untersuchungstechniken und dadurch differente Ergebnisse vermieden werden. Weiterhin wurden die meisten Interviews von zwei geschulten Untersuchern mit muttersprachlicher Kompetenz (OAC und ACR) vollzogen.

Bei Häfner et al. (2017) fokussierte man sich bei der Analyse der klinischen Daten vor allem auf die untere und obere Extremität. Im Rahmen der dermatoneurologischen Untersuchung konnten die meisten physischen Beeinträchtigungen bei den Augen gesehen werden, welche aufgrund der unterschiedlichen Untersuchungsbedingungen (wechselnde Untersuchungsorte mit unterschiedlichen Lichtverhältnissen) erschwert waren, was bei der Interpretation der Daten zu berücksichtigen ist. Eine Verschlechterung der Sicht kann ebenfalls Folge von anderen Erkrankungen, Umwelteinflüssen sowie des Alters sein und ist nicht pathogonomisch für die Lepraerkrankung wie z. B. die „Lepraflecken“ [51, 52].

Im Rahmen der Datenerhebung und der Analyse konnte festgestellt werden, dass die durch die lokalen *primary health care centres* erhobenen Daten und Patientenakten teilweise unvollständig waren. Es konnten fehlende Informationen zur Klinik, zur Klassifikation sowie zur GD am Diagnosetag gesehen werden.

Die Studie fand in einem für Lepra hoch endemischen Gebiet statt. Es wurden zusätzlich 128 Patienten in die Studie mit aufgenommen, die im nationalen Registrierungssystem für meldepflichtige Krankheiten (SINAN) nicht auftauchten, jedoch in den *local health care centres* aufgeführt waren. Bei Heukelbach et al. (2011) konnten weitere Therapieabbrecher identifiziert werden, die ebenfalls nicht im SINAN gemeldet waren. In den letzten Jahren war die Anzahl der Therapieabbrecher dank der Intensivierung des Leprakontrollprogrammes gesunken. Bei Heukelbach et al. (2011) wurden nur 28 Therapieabbrecher identifiziert, was die statistische Aussagekraft der Datenanalyse reduzierte.

Eine weitere Einschränkung zeigte sich im Hinblick auf die Nichtteilnahme, vor allem bei den Therapieunterbrechern. Da durch diese Nichtteilnahme ein

systematischer Fehler entstanden sein könnte, erfolgte eine weitere Auswertung der Daten, bei der das Kriterium für die Studienteilnahme bzgl. der Compliance der MDT modifiziert wurde, nämlich in der Therapieunterbrechung basierend auf der Therapiedauer. Die Analyse berücksichtigte hierbei nicht die MDT-Einnahme zuhause, sondern das Erscheinen zu den monatlichen überwachten Tabletteneinnahmen in den *health care centres*. Diese neue Einteilung sollte dementsprechend bei der Interpretation der Ergebnisse berücksichtigt werden.

3.4 Schlussfolgerungen

Die vorliegenden Arbeiten und das übergeordnete Studienprojekt Integrahans MAPATOPI sind für die Verbesserung der Kontrolle der Lepraerkrankung und ihrer Folgen bedeutsam. Es wird offenkundig, dass in den letzten Jahren das Gesundheitsministerium Brasiliens und das Gesundheitsministerium des Bundesstaates Tocantins viel in die Verbesserung des Leprakontrollprogramms investiert haben. Die Anzahl der Lepraneuerkrankungen und die Rate der Patienten, die die MDT abgebrochen oder unterbrochen haben, sind in den letzten Jahren gesunken. Dennoch weisen die beiden vorliegenden Publikationen auf weiterhin bestehende Probleme hin, wie z. B. den hohen prozentualen Anteil an Patienten an G1D/G2D unter den Neuerkrankungen sowie eine Verschlechterung des GDs nach Beendigung der MDT. In diesem Rahmen spielten die männliche Dominanz, die späte Diagnosestellung und der damit verspätete Therapiebeginn sowie die Phase nach Beendigung der MDT eine wichtige Rolle. Das bereits gut in die primäre Gesundheitsversorgung integrierte Leprakontrollprogramm muss weiter optimiert werden. Hierzu gehören die regelmäßige Schulung von medizinischem Fachpersonal, eine Verbesserung der Qualität der Datenerhebungen und Datenaufzeichnung sowie gute technische und fachliche Ausstattungen der Bezirke. Unabhängig von Alter und Geschlecht sollten systematische gesundheitsfördernde Maßnahmen in Schulen, aber auch in der Bevölkerung z. B. durch Kampagnen und Schulungen vollzogen werden, damit die Lepraerkrankung mit ihren Folgen und die Bedeutung einer frühen Diagnose stets im Bewusstsein gehalten werden.

Eine regelmäßige medizinische Kontrolle mit dermatoneurologischer Untersuchung nach erfolgreichem Abschluss der MDT sollte in die primäre Gesundheitsversorgung eingeführt werden. Die Risikogruppen für Ausbildung von Spätfolgen, zu denen u. a. Patienten des männlichen Geschlechts gehören, müssen vermehrt in das Gesundheitssystem integriert werden, damit die Leprainfektion bzw. auch andere Erkrankungen schneller diagnostiziert und behandelt werden können.

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5 Anhang

5.1 Erhebungsbogen der dermatoneurologischen Untersuchung

UNIVERSIDADE FEDERAL DO CEARÁ
FACULDADE DE MEDICINA
DEPARTAMENTO DE SAÚDE COMUNITÁRIA

PROJETO MAPATOPI:
Padrões epidemiológicos, clínicos, psicossociais e operacionais da hanseníase nos estados do Maranhão, Pará, Tocantins e Piauí: uma abordagem integrada.

Município: _____ **Nome:** _____

FACE	1ª / /		2ª / /		3ª / /	
Nariz	**D**	**E**	**D**	**E**	**D**	**E**
Queixa principal						
Ressecamento (S/N)						
Ferida (S/N)						
Perfuração de septo (S/N)						
Olhos	**D**	**E**	**D**	**E**	**D**	**E**
Queixa principal						
Fecha olhos s/ força (mm)						
Fecha olhos c/ força (mm)						
Triquíase(S/N) / Ectrópio(S/N)						
Dimin. sensib. córnea (S/N)						
Opacidade córnea (S/N)						
Catarata (S/N)						
Acuidade Visual						

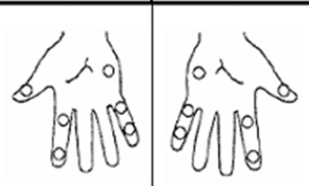
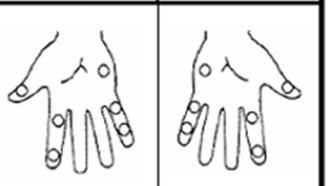
Membros Superiores	1ª / /		2ª / /		3ª / /	
Queixa principal						
Palpação de nervos	**D**	**E**	**D**	**E**	**D**	**E**
Ulnar						
Mediano						
Radial						

Legenda: N = normal E = espessado D = dor

Avaliação da Força	1ª / /		2ª / /		3ª / /	
	D	**E**	**D**	**E**	**D**	**E**
Abrir dedo mínimo Abdução do 5° dedo (nervo ulnar) 						
Elevar o polegar Abdução do polegar (nervo mediano) 						
Elevar o punho Extensão de punho (nervo radial) 						

Legenda: F=Forte D=Diminuída P=Paralisado ou 5=Forte, 4=Resistência Parcial, 3=Movimento completo, 2=Movimento Parcial, 1=Contração, 0=Paralisado

Inspeção e Avaliação Sensitiva

1ª / /		2ª / /		3ª / /	
D	**E**	**D**	**E**	**D**	**E**
					

Legenda: Caneta/filamento lilás(2g): Sente ✓ Não sente X ou Monofilamentos: seguir cores

Garra móvel: M Garra rígida: R Reabsorção:  Ferida:

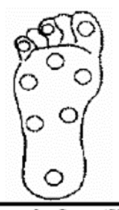
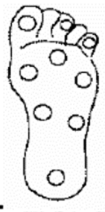
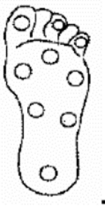
Fibular						
Tibial posterior						

Legenda: N = normal E = espessado D = dor

Avaliação da Força	1ª / /		2ª / /		3ª / /	
	D	E	D	E	D	E
Elevar o hálux Extensão de hálux (nervo fibular) 						
Elevar o pé Dorsiflexão de pé (nervo fibular) 						

Legenda: F=Forte D=Diminuída P=Paralisado **ou** 5=Forte, 4=Resistência Parcial, 3=Movimento completo, 2=Movimento Parcial, 1=Contração, 0=Paralisado

Inspeção e Avaliação Sensitiva

1ª / /		2ª / /		3ª / /	
D	E	D	E	D	E
					

Legenda: Caneta/filamento lilás(2g): Sente ✓ Não sente **X** **ou** Monofilamentos: seguir cores

Garra móvel: M Garra rígida: R Reabsorção:  Ferida:

CLASSIFICAÇÃO DO GRAU DE INCAPACIDADE (OMS)

DATA DA AVALIAÇÃO	OLHOS		MÃOS		PÉS		MAIOR GRAU	ASSINATURA
	D	E	D	E	D	E		
Aval. diagnóstico / /								
Aval. de alta / /								

LEGENDA PARA PREENCHIMENTO DO GRAU DE INCAPACIDADES

GRAU	CARACTERÍSTICAS
0	Nenhum problema com os olhos, mãos e pés devido à hanseníase.
I	Diminuição ou perda da sensibilidade nos olhos. Diminuição ou perda da sensibilidade nas mãos e /ou pés. (não sente 2g ou toque da caneta)
II	Olhos: lagoftalmo e/ou ectrópio; triquíase; opacidade corneana central; acuidade visual menor que 0,1 ou não conta dedos a 6m. Mãos: lesões tróficas e/ou lesões traumáticas; garras; reabsorção; mão caída. Pés: lesões tróficas e/ou traumáticas; garras; reabsorção; pé caído; contratura do tornozelo.

MONOFILAMENTOS

COR	Gramas
Verde	0,05
Azul	0,2
Lilás	2,0
Verm. Fechado	4,0
Verm. Cruzado	10,0
Verm. Aberto	300,0
Preto	s/resposta

5.2 Erhebungsbogen der soziodemographischen und klinischen Daten

ID FAM:_____ **/ ID IND:**_____

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FICHA PRONTUÁRIO - DIAGNÓSTICO, TRATAMENTO, ALTA (Ficha 1)

Município:_____ **Unidade de Saúde:**___ _____

Data preenchimeto:_____ **Preenchido por:**_____

1- DADOS DO PACIENTE				
Nome do Paciente: _____				**No. prontuário:**_____
Data Nascimento:_____/_____/_____ ou **Idade:**_____				**Sexo:** **(1)** Masculino **(2)** Feminino
Escolaridade:_____ (9) Não informado *(=em banco no prontuário)*				
Ocupação:_____ (9) Não informado				
Endereço (Rua; número):_____				
Bairro:_____	**Zona: (1)** Urbana **(2)** Rural			**CEP:**_____
2- SITUAÇÃO DE PACIENTE:				
(1) Tratamento	**(2)** Alta por cura	**(3)** Faltoso	**(4)** Abandono	**(5)** Transferido
3- DADOS DIAGNÓSTICO				
Data do Diagnóstico (dia/mês/ano):_____/_____/_____ (9) Não informado				
Número de lesões cutâneas: _____ (9) Não informado				**Número de nervos acometidos:** _____ (9) Não informado
Forma clínica da doença no diagnóstico:	**(1)** Indeterminada	**(2)** Tuberculóide	**(3)** Dimorfa	
	(4) Vichowiana	**(5)** Não Classificada	**(9)** Não informado	
Classificação operacional da doença:	**(1)** Paucibacilar	**(2)** Multibacilar	**(9)** Não informado	
Grau de incapacidade:	**(0)** Grau Zero	**(1)** Grau I	**(2)** Grau II	**(3)** Não Avaliado **(9)** Não informado
Modo de Detecção:	**(1)** Encaminhamento	**(2)** Demanda Espontânea	**(3)** Exame de Coletividade	
	(4) Exame de Contatos	**(5)** Outro modo:_____	**(9)** Não informado	
Basciloscopia:	**(1)** Positivo	**(2)** Negativo	**(3)** Não realizado	**(9)** Não informado
Data do inicio do tratamento (dia/mês/ano):_____ (9) Não informado				
Esquema terapêutico inicial:	**(1)** PQT/PB/6 doses	**(2)** PQT/MB/12 doses	**(3)** PQT/MB/24 doses	
	(4) ROM	**(5)** Outros Esquemas Alternativos	**(9)** Ignorado	
CONTATOS:	**Numero de contatos examinado**:_____		**Numero de contatos registrados**: _____	
	Numero de contatos suspeitos:` _____		**Numero de contatos positivo:** _____	
5- DADOS ALTA				
Data da ultima dose (dia/mês/ano):_____		**Data da alta** (dia/mês/ano):_____		
Forma clínica da doença:	**(1)** Indeterminada	**(2)** Tuberculóide	**(3)** Dimorfa	
	(4) Vichowiana	**(5)** Não Classificada	**(9)** Não informado	
Classificação operacional da doença:	**(1)** Paucibacilar	**(2)** Multibacilar	**(9)** Não informado	
Grau de incapacidade:	**(0)** Grau Zero	**(1)** Grau I	**(2)** Grau II	**(3)** Não Avaliado **(9)** Não informado
6- REAÇÃO DIAGNÓSTICO/ TRATAMENTO:	**(1) Sim –** *preencher* ***Ficha Reação***	**(0)** Não	**(9)** Não informado	
6-1 REAÇÃO PÓS-ALTA?	**(1) Sim –** *preencher* ***Ficha Reação***	**(0)** Não	**(9)** Não informado	

Observações:_____

5.3 Erhebungsbogen für die Leprareaktionen

ID FAM / ID IND:_____

UNIVERSIDADE FEDERAL DO CEARÁ
FACULDADE DE MEDICINA/DEPARTAMENTO DE SAÚDE COMUNITÁRIA

PROJETO MAPATOPI: Padrões epidemiológicos, clínicos, psicossociais e operacionais da hanseníase nos estados do Maranhão, Pará, Tocantins e Piauí: uma abordagem integrada.

FICHA PRONTUÁRIO – REAÇÃO (Ficha 2)

OBS.: Para cada reação hansênica identificada, preencher uma Ficha de Reação

Município:_____ **Unidade de Saúde:**_____

Data preenchimeto:_____ **Preenchido por:**_____

1- DADOS DO PACIENTE				
Nome do Paciente: _____			**No. prontuário:**_____	
2- DADOS REAÇÕES				
Data do episódio reacional (dia/mês/ano):_____/_____/_____		(9) Não informado (=não informado no prontuário)		
Situação do paciente no episódio de reação	(1) Caso novo	(2) Tratamento	(3) Abandono	
	(4) Pós- Alta	(9) Não informado		
Tipo de reação:	(1) Reação Tipo I (Reversa / RR)		(2) Reação Tipo II (Eritema Nodoso / ENH)	
	(3) Neurite isolada (Pura)		(9) Não informado	
Tratamento inicial realizado	(1) Sim	(2) Não	(9) Não informado	
Medicamentos utilizados:	**Prednisona:**	(1) Sim	(0) Não	(9) Não informado
	Talidomida:	(1) Sim	(0) Não	(9) Não informado
	Outros medicamentos:_____			
3- DADOS NEURITES				
Desenvolveu neurites	(0) Não	(1) Unilateral	(2) Bilateral	(9) Não informado
Localização da neurite – Membros Superior	(1) N. Ulnar	(2) N. Mediano	(3) N. Radial	(9) Não informado
Localização da neurite – Membros Inferiores	(1) N. Fibular	(2) N. Tibial Posterior		(9) Não informado
Tratamento para neurites	**Prednisona:**	(1) Sim	(2) Não	(9) Não informado
	Se SIM Prednisona, qual dose INICIAL:_____			
	Anti-inflamatório não-hormonal (ANH):	(1) Sim	(2) Não	(9) Não informado
Imobilizou	(0) Não	(1) Sim	(9) Não informado	
Foi realizado avaliação sensitiva-motora (Ficha Avaliação Neurológica Simplificada)?	(0) Não	(1) Sim	(9) Não informado	

Observações:_____

5.4 Erhebungsbogen zur familiären Situation

ID FAM:_____

UNIVERSIDADE FEDERAL DO CEARÁ
FACULDADE DE MEDICINA/DEPARTAMENTO DE SAÚDE COMUNITÁRIA

PROJETO MAPATOPI: Padrões epidemiológicos, clínicos, psicossociais e operacionais da hanseníase nos estados do Maranhão, Pará, Tocantins e Piauí: uma abordagem integrada.

FICHA FAMILIAR (Ficha 3)

Estado: TO	**Município:**_____	**UBS:**_____
Nome do paciente: _____		**ID IND** _____
Nome do paciente: _____		**ID IND** _____
Data preenchimento: ____/____/_____		**Preenchido por:**_____

1 - CONDICÕES DA MORADIA			
1. De que material é feita sua casa? *(Tipo de casa)*	**(1)** Tijolo/adobe	**(2)** Taipa revestida	**(3)** Taipa não-revestida
	(4) Madeira	**(5)** Material aproveitado	**(6)** Outros_____
2. Número de cômodos (salas, quartos, banheiros, cozinhas): _____			
4. Quantas pessoas moram atualmente na casa? _____			
5. Zona de residência:	**(1)** Rural	**(2)** Urbana	**(3)** Outros, qual?_____
6. Energia elétrica:	**(0)** Não	**(1)** Sim/CELTINS	
7. Destino do lixo:	**(1)** Coleta publica/Carro passa	**(2)** Céu aberto queima	**(3)** Céu aberto não queima
	(4) Enterra	**(5)** Outros:_____	
8. Na sua casa é?... *(Destino das fezes/urina)*	**(1)** Esgoto (rede publica)/ SANEATINS	**(2)** Fossa	**(3)** Céu aberto
			(4) Outros:_____
9. Abastecimento de água	**(1)** Rede publica geral	**(2)** Poço profundo (ou nascente)	**(3)** Outros_____
10. *Renda mensal familiar*	_____	**(0)** Não sabe	**(9)** Não quis informar

SERVIÇOS DE SAÜDE NO BAIRRO DE RESIDENCIA			
Quando foi última visita Agente Comunitário de Saúde (ACS)? *(Há quantos dias atrás?)*	_____	(0) Nunca visitou	(1) Não lembra
		(2) Não está em casa qdo ele passa	(3) Não sabe dizer

Observação: _____

5.5 Erhebungsbogen von persönlichen Daten

ID FAM:_____/ ID IND:_____

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FICHA INDIVIDUAL (Ficha 4)

Estado: TO Município:_____ UBS:_____

Data preenchimento: ____/____/_____ Preenchido por:_____

A- DADOS DO PACIENTE

1-Nome do Paciente:_____

2-Data Nascimento: ____/____/_____ *ou* Idade:_____ (anos)

3-Sexo: (1) Masculino (2) Feminino

4-Estado civil: (1) Solteiro (2) Casado/Mora junto (3) Separado/Divorciado (4) Viúvo

5-Escolaridade: _____ (0) Analfabeto (1) 1ª a 4ª serie Inc EF (ou do Primário/1° grau) (2) 4ª serie Comp. EF (ou do Primário/1° grau) (3) 5ª a 8ª serie Inc EF (ou do Ginásio/1° grau) (4) Ens. Fundamental Comp. (Ginásio/1° grau) (5) Ensino Médio Incompleto (Colegial/2° Grau) (6) Ensino Médio Completo (Colegial/2° Grau) (7) Educação Superior Incompleta (3° grau Inc) (8) Educação Superior Completa (3° grau) (9) Não sabe

6-Trabalha atualmente: (1) Sim (2) Desempregado (3) Trabalho esporádico/bicos (4) Aposentado, não trabalha* (5) Aposentado, faz bicos* (6) Pré-escolar/estudante (7) Outros:_____

7-Ocupação/Trabalha/Ihou com o que? *(especificar para todas as situações, exceto 6)* _____

8-Condição atual do paciente: (1) Em tratamento (2) Alta (3) Outros:_____

9-Você sabe o nome da doença de pele que você trata/tratou no posto? (1) Hanseníase* (2) Lepra* (3) Outro*:_____ (4) Não sabe

10-*Quais outros nomes você conhece para esta mesma doença? _____

B – MIGRAÇÃO

11-Local de nascimento Cidade:_____ Estado:_____

12-Há quanto tempo mora neste casa? _____(anos) _____(meses) _____(dias)

13-Depois que você teve diagnóstico de hanseníase você se mudou? (0) Não (1) Sim (3) Não lembra

13.1- Se SIM, para onde se mudou? (1) Outro bairro: qual?_____ (2) Outra cidade/UF?_____

14-Se SIM, por que se mudou?_____

15-Antes do diagnóstico de hanseníase, você morava em outras cidades? (0) Não (1) Sim (3) Não lembra

16-Onde morou nos 5 anos antes do diagnóstico de hanseníase?

(ano diag 2006 – onde morava em 2001?)	Cidade1:_____	UF1:_____	Tempo1:_____
(ano diag 2007 – onde morava em 2002?)	Cidade2:_____	UF2:_____	Tempo2:_____
(ano diag 2008 – onde morava em 2003?)	Cidade3:_____	UF3:_____	Tempo3:_____
	Cidade4:_____	UF4:_____	Tempo4:_____

C – SERVIÇOS DE SAÚDE – Acesso

17-Qual(is) o(s) meios utilizados para chegar neste/no serviço de saúde que você fez/faz tratamento para sua doença de pele/hanseníase? (1) A pé (2) Bicicleta (3) Moto (4) Carro (5) Barco (6) Outro:_____

18-Quanto tempo você leva para chegar neste/no serviço que faz o tratamento? _____(horas) _____(minutos)

19-Você acha difícil o acesso para chegar neste/no serviço que você faz o tto? (0) Não (1) Sim*, por que? (3) Não sabe dizer

20-Se SIM, por que acha difícil?_____

D – DIAGNÓSTICO (dg)			
21-Antes de ter o diagnóstico, já tinha ouvido falar em hanseníase (ou desta doença de pele)	(0) Não	(1) Sim	(3) Não sabe dizer
22-Antes de ter o diagnóstico, conhecia alguém com hanseníase?	(0) Não	(1) Sim*	(3) Não sabe dizer
23-Se SIM, quem era(m)?	(1) Pai/Mãe	(2) Irmão/Irmã	(3) Avó/Avô
	(4) Outros, quem:_____		
24-Como achou que estava c/hanseníase (ou doente da pele)?_____			
25-Qual o nome do serviço de saúde que foi feito o diagnóstico?_____			
26-Antes do diagnostico neste serviço, você procurou outros serviços para saber o que tinha?	(0) Não	(1) Sim*	(3) Não se lembra
27-Se SIM, quais os nomes dos serviços?	US1:_____		(3) Não se lembra
	US2:_____		(3) Não se lembra
	US3:_____		(3) Não se lembra
	US4:_____		(3) Não se lembra
28-Antes de ter o diagnóstico, procurou outros tratamentos (além do posto)?	(0) Não	(1) Sim*	(3) Não se lembra
29-Se SIM, que tipo?_____			
30-Desde que percebeu/indicaram sintomas (machas/dor/dormência/etc), quanto tempo levou para procurar atendimento?	_____ (anos)	_____ (meses)	_____ (dias)
			(3) Não se lembra
31-Por que demorou este tempo?_____			
E – TRATAMENTO/ABANDONO			
32-Como era o consumo de bebida alcoólica (antes e durante o tratamento):_____			
33- Parou de beber por causa do tratamento?	(0) Não	(1) Sim	(3) Não se sabe
33.1- Atualmente, você toma bebida alcoólica?	(0) Não	(1) Sim*	
34- Se SIM, que tipo de bebida alcoólica você bebe atualmente?	(0) Nenhuma	(1) Cerveja	(2) Cachaça
	(3) Whisky/Vodka	(4) Rum	(5) Vinho
	(6) Outros:_____		
35- Se SIM, com que freqüência você bebe uma destas bebidas atualmente?	_____ (dias)	(0) Não se aplica	
36-Você tem dificuldade de tomar/engolir o remédio do tratamento da pele/hans?	(0) Não	(1) Sim	(3) Não sabe dizer
37-Durante o tratamento da pele/hanseníase com o remédio da cartela, alguma vez faltou remédio no serviço de saúde para você?	(0) Não	(1) Sim	(3) Não lembra
38-Em algum momento do seu tratamento da hanseníase (com a cartela), você parou de tomar o remédio?	(0) Não	(1) Sim*	(3) Não lembra
39-Se SIM, por que parou?_____			
40-Se SIM, por quanto tempo parou?	_____ (anos)	_____ (meses)	_____ (dias) (3) Não lembra
F – REACOES			
41-Desde quando começou o tratamento, teve alguma reação?	(0) Não	(1) Sim*	(3) Não sabe dizer
42-* Se SIM, o que você teve?_____			

G – ALTA			
43-*Paciente em alta?*	(0) Não	(1) Sim	(3) Não sabe dizer
44-Quando terminou o tratamento com a cartela/PQT, você teve que procurar o serviço por causa da hanseníase de novo?	(0) Não*	(1) Sim	(3) Não sabe dizer
45-Se SIM, por que motivo? _____			
46-Se SIM, quanto tempo depois da alta? _____ (anos) _____ (meses) _____ (dias)			(3) Não lembra
H – CONTATOS			
47-Quando começou o tratamento da hanseníase, algum profissional de saúde do serviço lhe informou que as pessoas que moravam na sua casa deveriam ser examinadas também?	(0) Não	(1) Sim	(3) Não lembra
48-Quando começou o tratamento, você contou para as pessoas que moravam na sua casa que você tinha hanseníase/a doença de pele?	(0) Não*	(1) Sim	(3) Não lembra
49-Se NÃO, por que não contou? _____			
I – CONHECIMENTO/CRENÇAS			
50-Para as pessoas que você contou que tinha hanseníase, você acha que elas te tratam diferente ou da mesma forma? _____			
51-Você acha que a hanseníase tem cura? Por quê? _____			

5.6 Einverständniserklärung der Studienteilnehmer auf Portugiesisch

(1) TERMO DE CONSENTIMENTO LIVRE E ESCLARECIDO*

"Padrões epidemiológicos, clínicos, psicossociais e operacionais da hanseníase nos estados do Maranhão, Pará, Tocantins e Piauí: uma abordagem integrada".

**Pacientes*

Prezado Sr./Sra,
Você está sendo convidado a participar de uma pesquisa. Sua participação é importante, porém, você não deve participar contra a sua vontade. Leia atentamente as informações abaixo e faça qualquer pergunta que desejar, para que todos os procedimentos desta pesquisa sejam esclarecidos.

Esta pesquisa avalia quantas pessoas têm hanseníase e qual a situação clínica destas pessoas, quais os motivos que fazem uma pessoa abandonar o tratamento ou demorar a procurar o serviço de saúde para se tratar; como as pessoas se sentem na sua vida em comunidade (amigos/família/trabalho) em relação à doença. Além disto, a pesquisa avalia como os serviços de saúde e o programa de controle da hanseníase estão funcionando.

Endereço do responsável pela pesquisa

Instituição: Departamento de Saúde Comunitária da Faculdade de Medicina da Universidade Federal do Ceará

Pesquisador Responsável: Prof. Dr. Jorg Heukelbach e demais pesquisadores incluídos no estudo

Endereço: R. Prof. Costa Mendes, 1608; Bloco didático/ 5º andar – Bairro: Rodolfo Teófilo – Fortaleza/CE

CEP 60430-140

Telefones p/contato: (85) 3366-8045 / 3366-8044

ATENÇÃO: Para informar ocorrências irregulares ou danosas durante a sua participação no estudo, dirija-se ao:

Comitê de Ética em Pesquisa da Universidade Federal do Ceará

Rua Coronel Nunes de Melo, 1127 Rodolfo Teófilo

Telefone: 3366.8338

Antes de decidir a respeito de sua participação, é importante que você saiba o motivo da realização desse estudo e o que ele envolverá. Pergunte-nos caso haja algo que não esteja claro ou caso necessite de maiores informações. Você dispõe de tempo para pensar se desejará participar ou não do estudo. Os profissionais envolvidos nesse estudo não são remunerados para a realização desta pesquisa. O estudo foi revisado por um Comitê de Ética em Pesquisa independente da Instituição Responsável.

Neste estudo serão realizadas entrevistas, serão aplicados questionários e serão realizados exames clínicos.
Caso você tenha diagnóstico de hanseníase o exame será uma avaliação neurológica simplificada, isto é, será feito exame clínico dos olhos e do nariz; avaliação dos principais nervos dos braços, mãos, pernas e pés através do toque com as mãos (palpação) e avaliação da sensibilidade das mãos e pés e também avaliação de força muscular.
A avaliação clínica levará 30 minutos, questionários 15 minutos e a entrevista 30 minutos

RISCOS E BENEFÍCIOS

- Nesse estudo, NÃO haverá procedimentos de coleta de sangue, fezes, urina, pele ou outros procedimentos invasivos que gerem riscos diretos ao participante. Você NÃO ESTARÁ SUJEITO A NENHUM RISCO caso concorde em participar desta pesquisa.
- Você não receberá nenhum pagamento por participar desse estudo.

DIREITOS DOS PARTICIPANTES:

- A garantia de receber a resposta ou esclarecimento a qualquer pergunta ou dúvida a cerca dos procedimentos, riscos, benefícios e outros assuntos relacionados com a pesquisa.
- A liberdade de retirar meu consentimento a qualquer momento e deixar de participar do estudo sem que isso traga prejuízo a minha pessoa.
- A segurança de que não será identificado e que será mantido o caráter confidencial da informação relacionada com minha privacidade.
- Receber informações atualizadas durante o estudo, ainda que este possa afetar a minha vontade do participante de continuar na pesquisa.

CONSENTIMENTO DA PARTICIPAÇÃO DA PESSOA COMO SUJEITO OU
DECLARAÇÃO DO PARTICIPANTE OU DO RESPONSÁVEL PELO PARTICIPANTE:

Tendo compreendido perfeitamente tudo o que me foi informado sobre a minha participação no mencionado estudo e estando consciente dos meus direitos, das minhas responsabilidades, dos riscos e dos benefícios que a minha participação implica, concordo em dele participar e para isso eu DOU O MEU CONSENTIMENTO SEM QUE PARA ISSO EU TENHA SIDO FORÇADO OU OBRIGADO.

Fortaleza, _____/_____/_____

_____ *Assinatura ou impressão datiloscópica* *d(o,a) voluntári(o,a) ou responsável legal*	_____ *Nome e Assinatura do(s) responsável(eis) pelo estudo* _____ *Nome do profissional que aplicou o TCLE*

Endereço d(o,a) participante-voluntári(o,a)

Domicílio: (rua, praça, conjunto): _____

Complemento (no.):_____ Bairro: _____ Cidade:_____UF:__

Ponto de referência _____CEP_____

Telefone:_____

Danksagung

Ich bin sehr dankbar darüber, dass ich die Möglichkeit bekommen habe, ein Teil dieses einzigartigen Projektes sein zu dürfen. Mir wurde dadurch ein eindrucksvoller Lebensabschnitt mit einzigartigen Begegnungen und Erfahrungen geschenkt, der mich sehr geprägt hat und von dem ich in meinem weiteren Leben zehren werde.

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Maria de Jesus Freitas de Alencar schulte uns in der dermatoneurologischen Untersuchung der Leprapatienten, wofür ich mich bedanke.

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Zuletzt möchte ich Prof. B. Heller danken, die mir den Weg in die Medizin geebnet hat und mich immer motiviert hat, meinen Träumen zu folgen. Requiescat in pace.