THE PATTERNS OF LEPROSY AT CHRIS HANI BARAGWANATH ACADEMIC HOSPITAL

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A research report submitted to the Health Sciences, University of the Witwatersrand, in partial fulfillment of the requirements for the degree of Master of Medicine in Dermatology.

Johannesburg 2020

DECLARATION

I, Lindinkululeko Jabulile Nkehli declare that this research report is my own work which is being submitted for the degree of Master of Medicine (in the submissible format with my protocol and an extended literature review) in the branch of Dermatology at the University of Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other University.

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20...day of…November…..2020

DEDICATION

I dedicate this research to my three daughters Lelona, Lulutho and Lizalise for teaching me patience; giving me a reason to confront my daily challenges and allowing me time to complete this project.

To my family, my mother, my brothers and sisters for their constant love and endless support which granted me the courage to finish this project.

To The Almighty God, who has granted me the gift of life and strengthen me in times of trials.

ACKNOWLEDGEMENTS

I would like to extend my appreciation to Professor Colin Menezes and Dr. Merika Tsitsi for encouraging, supporting and guiding me to the completion of my research.

My sincere gratitude goes to Professor Joy Schulz who did not only teach me dermatology from basics, but also instilled in me the love of the study of leprosy, and shared her world of knowledge and experience on the subject throughout my dermatology post-graduate training and beyond.

ABSTRACT

Background

The World Health Organization announced a strategy to eliminate childhood leprosy infections, visible deformities and discriminatory legislation against leprosy patients by 2020. However, challenges in achieving a leprosy-free world and preventing neurological sequelae still exist. Human immunodeficiency virus (HIV) infection has been a challenging burden in our population. HIV-leprosy co-infection may result in an increased frequency of leprosy reactions without affecting the spectrum of leprosy. From 1921 to 1997 the leprosy prevalence remained less than one patient per 10 000 population. Current South African literature has very scanty information regarding the current situation of leprosy.

Objectives

The purpose of this research was to describe the trend of new leprosy patients from 1999 to 2015, including the demographics, clinical spectrum and treatment outcomes of patients treated for leprosy at Chris Hani Baragwanath Academic Hospital (CHBAH) during this period.

Methods

A retrospective review of patients' clinical records was undertaken. Data on demographics, clinical spectrum including the leprosy classification, reactions, neurological involvement, HIV infection association as well as treatment outcomes were extracted. Data analysis was performed using descriptive and inferential statistics and a time series analysis.

Results

An upward trend from 1999 to 2001 was followed by a decline in the number of new patients. Eighty patients were registered over a period of 17 years, with a male-to-female ratio of 3:1. Thirty six patients were immigrants. Five were children less than 15 years old. Multibacillary leprosy was the most common type with 71 patients. Thirty six patients were lepromatous leprosy subtype, 22 were borderline-lepromatous, 13 were borderline-tuberculoid, six were midborderline and three were tuberculoid leprosy. Thirty one patients presented with reactions, type 1 in nine patients and type 2 in 21 patients with both types in one patient. Grade 2 neurological deformities were diagnosed in 37 patients, of which two were children. Eight patients were found to have HIV-leprosy co-infection. Out of 52 patients who completed treatment, 26 were cured and 26 were lost to follow-up. Twenty-one patients defaulted treatment while three patients relapsed.

Conclusion

This study highlights current status of leprosy in a low endemic centre with declining numbers of new patients. Multibacillary forms with grade 2 disabilities are common. The constant emergence of leprosy in our population highlights shortfalls in our control campaigns. Furthermore, a high rate of grade 2 disabilities necessitates scrutiny of education directed at early patient detection and follow-up strategies.

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ABBREVIATIONS

BB	Midborderline leprosy
BI	Bacillary index
BL	Borderline lepromatous leprosy
BT	Borderline tuberculoid leprosy
CD4 count	Cluster of differentiation 4 count
CHBAH	Chris Hani Baragwanath Academic Hospital
ENL	Erythema nodosum leprosum
G2D	Grade-2 disabilities
HIV	Human immunodeficiency virus
LL	Lepromatous leprosy
M. leprae	*Mycobacterium Leprae*
MB	Multibacillary
MDT	Multidrug treatment
MI	Morphological index
NBAA	Number of body areas affected
PB	Paucibacillary
RJC	Ridley and Jopling classification
SA	South Africa
TT	Tuberculoid leprosy
WHO	World Health Organization

CHAPTER 1: PROTOCOL WITH EXTENDED LITERATURE REVIEW

1.1. Introduction

Leprosy as a global public health problem has been studied widely. The neurological complications of the disease are common. Since 1991, there has been a successful campaign to eliminate leprosy worldwide.(1) In 2016, the World Health Organization (WHO) announced the Global Leprosy Strategy 2016-2020, to reduce childhood infections, grade-2 disabilities (G2D), and discriminatory legislation against leprosy patients.(1, 2) This was ultimately to achieve zero leprosy infections worldwide.(1, 3)

Leprosy, also known as Hansen's disease, is a *Mycobacterium leprae (M. leprae)* infection. The infection is transmitted through droplet spread and targets the skin, mucosal surfaces and the nervous system.(4) It has a predilection for macrophages and nerves.(4) The bacillus is weakly acid fast and thrives best in temperatures below 30°C.(5) The bacteria multiplication is very slow with incubation periods as long as two to ten years. *M. leprae* has not been cultured successfully in vitro but can be cultivated in armadillo footpads.(3)

1.2. Trends

Important epidemiological indicators of disease burden in leprosy are new case detection rate and prevalence rate. In areas of high endemicity of leprosy, as seen in parts of India and Brazil, the new case detection rate and or prevalence rate are more than 10 cases per 100 000 inhabitants and one case per 10 000 inhabitants respectively.(6-9) The highest incidence of the disease is found in India, Brazil and Indonesia, which together accounted for just over 80 percent of new patients in 2016 and 2017.(1, 2) About 210 671 new patients were reported from 150

countries in 2017, little change from 2014 statistics of more than 200 000 new patients globally.(2) The number of new patients from India, which contributes 60 percent of global incidence, stabilised between 2007 and 2016, recording 137 685 and 135 485 respectively.(10) Some individual countries and centres reported a declining trend while others recorded increasing numbers of new patients.(2) Puchner *et al*. showed a declining trend of new patients in low endemic area of Sudan from 2010 to 2016, which was similar to trends reported in Iran from 2005 to 2015. (8, 11)

In 2015 and 2016 Africa had nine percent of patients in the global leprosy incidence.(1) The Democratic Republic of Congo and Ethiopia are the top two countries with the leprosy burden in Africa.(1)

In South Africa (SA) a decreasing trend of new leprosy patients has been observed from the late 1950s.(12) From 1921 to 1997 the leprosy prevalence remained less than one patient per 10 000 population.(12) Following this period there is paucity of information on the trend of leprosy in SA.(1) In 2015 there were 35 new reported patients of leprosy in SA, 20 of which were foreign-born. However, the duration of their stay in the country prior to the diagnosis was unknown.(13, 14)

1.3. Demographics

Women form the minority of reported leprosy patients worldwide. It is still unclear whether this is a true reflection of the actual disease profile or a late presentation. Various treatment centres have reported a high male to female ratio.(15-17) This has been attributed to men migrating to cities in search of better employment.(15) A systematic review by Price *et al*., which analysed data from multiple countries, suggested that the male predominance may be due to late detection

in female patients.(10) In Indonesia, women have preference for religious and spiritual healers which contributes to the late presentation.(10)

Muthuvel *et al.* reported a mean age of presentation of 30.3±14.2 years.(15) The numbers of children younger than 15 years infected with leprosy remain low worldwide.(1, 2, 4, 15) Overall decline in childhood cases follow patterns similar to global trends as reported in both high and low endemic regions.(1, 2) In the low endemic region of Southern Brazil new childhood infections dropped from 3.0 percent (41 out of 1 354) to 1.9 percent (90 out of 4 770) for the periods 1982-1988 and 1990-2011 respectively.(4) Whenever increases in childhood cases have been recorded, like in Mumbai from 3 percent (2 out of 60) to 18 percent (13 out of 74) in 2008 and 2015 respectively, it is a sign of recent active disease transmission.(15)

In 2017, foreign-born new patients were reported in 30 countries (862 out of 32 673 patients).(2) In some countries like Qatar and United Arab Emirates all new cases were foreign-born in 2016.(1) This information becomes essential in planning effective surveillance programmes.(2)

A mosaic distribution of leprosy in SA was noted from 1981 to 1991.(12) New reported patients were clustered in Mpumalanga and northern KwaZulu-Natal.(12)

1.4. Contact

The single most important risk factor in the development of leprosy is close prolonged contact with a leprosy patient.(8) This increases the risk by five to eight times.(11) Contact-tracing has been used historically as a tool in detecting leprosy patients early.(8) This method was used to diagnose patients in Ermelo District in SA.(12) In Northern and Eastern Sudan, vigorous contact tracing of 3201 patients led to detection of 50 new patients between 2010 and 2016. However, it

did not indicate an increase the incidence of the disease.(8) Richardus *et al.* found that a higher percentage (62%) of new leprosy patients had a family history of leprosy contact in a low endemic area compared to a high endemic area (25%).(17)

1.5. Clinical spectrum

Leprosy presents as a spectrum of clinical variants which differ in shape, number and distribution of skin lesions.(3) Skin patches may be anaesthetic, hypopigmented, or reddish in association with enlarged peripheral nerves.(18) Sensory loss or weakness along the nerve supply may be found.(18)

Different classifications are used to differentiate between clinical variants.(19) These include the WHO operational classification, the Ridley and Jopling classification (RJC), the Madrid classification, and the classification describing the number of body areas affected by skin and neural lesions (NBAA).(19, 20) The WHO operational classification classifies patients with up to five skin lesions as paucibacillary (PB) and those with more than five lesions as multibacillary (MB). This classification has its shortcomings.(20) Rodrigues *et al,* showed that the use of this classification resulted in overestimation of MB form which was 42.9 percent compared to 36.8 percent when the RJC was used.(20)

The RJC divides the leprosy variants into two polar forms, tuberculoid leprosy (TT) and lepromatous leprosy (LL), as well as intermediate forms, which are subdivided into borderline tuberculoid leprosy (BT), midborderline leprosy (BB), and borderline lepromatous leprosy (BL).(3, 19, 20) In practice, these variants have overlapping clinical, immunological and histological features. The number of skin lesions increases from one to a few, in TT, to numerous and symmetrical towards the LL. Bacilloscopy, expressed as a bacillary index (BI) ranges from

1+ to 6+ and the morphological index (MI) shows the presentation of *M. leprae* as intact, fragmented or granular. (18, 19) BI is generally negative or weakly positive in TT and BT compared to positive in BB, BL and LL.(18, 19) Histological features include tuberculoid granulomas in TT and BT, less organised granulomas with some foamy macrophages in BB, and foamy macrophages containing many clumps of bacilli in BL and LL.(19, 21) The problem with the RJC is that the clinical and histological findings may not correlate.(19) This poses difficulties in classifying patients.(20)

Indeterminate leprosy, which is the initial stage of the disease, often poses a diagnostic challenge.(3, 19) It presents with single or multiple hypopigmented macules with no infiltration, erythema, anaesthesia or nerve thickening.(3) Histopathological findings are nonspecific and BI is negative.(3, 19) This is often an uncommon clinical presentation, as highlighted by Dacso *et al.* who found it in just one out of 158 patients.(7)

New leprosy patients are predominantly MB. In 2015 the total proportion of MB patients worldwide was 60.2 percent (126 783 out of 210 758), and in 2016 it was 59.1 percent (127 013 out of 214 783).(1, 13) The MB forms correspond to lepromatous and borderline forms.(4, 20) The proportion of new MB patients was 60 percent in the Democratic Republic of Congo and 80 percent in Ethiopian 2016.(1) The LL and BL, which always fall under MB leprosy, predominated by 77.5 percent per year in a Southern Brazilian study in the 1980s compared to 80.4 percent per year in the period of 1990-2011.(4)

Leprosy reactions represent acute hypersensitivity to the *M. leprae* antigen.(22) They can occur before, during or after multidrug treatment (MDT) is completed.(22, 23) There are two major types, type 1 and type 2. If a type 1 reaction occurs during MDT it is known as an upgrading or

reversal reaction, while those due to a of shift borderline forms towards the lepromatous pole are called downgrading reactions.(21, 23) Type 1 reactions are common in the borderline forms as they are immunologically unstable.(22, 23) Type 1 reactions are mediated by cellular immunity with the T-helper 1 response.(22) Acute inflammation and oedema of skin lesions which may ulcerate occur.(22) In a review, Kahawita *et al.* demonstrated a varying type 1 reaction prevalence rate ranging from 19 to 29 percent.(24)

A type 2 reaction, also known as erythema nodosum leprosum (ENL), results from T-helper 2 responses with immune complex deposition.(22) High bacillary loads, BI >4, as seen in LL, are associated with the development of type 2 reactions.(22, 23) Chhabra *et al.* presented a study with more patients presenting with a type 1 reaction (258 out of 849) compared to a type 2 reaction (60 out of 849), where BT patients predominated by 56.3 percent.(25)

Neurological involvement can occur in all forms of leprosy.(3) Even though in TT, skin lesions are few, severe sensory and motor neuropathy on the extremities and face may result. Nerve thickening is, asymmetrical, palpable and tender.(3) This may cause change in sensitivity leading to anaesthesia with trophic ulcers, bone resorption of digits and flexion deformities.(3) In LL, the neurological involvement is usually late and symmetrical due to poor perineural inflammation.(3) Glove and stocking sensory loss is typical. Trophic ulcers, osseous resorption and severe eye involvement may be seen.(3)

Neurological involvement is represented by disability grade.(26) For peripheral nerve involvement, grade 0 represents no functional impairment, grade 1 corresponds to anaesthesia of hands or feet with no visible deformity, and grade 2 is presence of both anaesthesia and visible deformities which are trophic ulcers, claw deformities and bone resorption of the extremities.(26)

For the eyes, grade 0 is no vision loss related to leprosy, grade 1 is some visual impairment (vision 6/60 or better) and grade 2 is severe loss of vision.(26)

Global decrease in new patients with G2D was observed from 2013 to 2017.(2) Of concern is that some countries like Cote d'Ivoire and Brazil reported increases of these patients from 2016 to 2017.(2) The number of new patients with G2D in the South East Asia region was 4.6 percent (7 398 out of 161 263) in 2016 of which 0.9 percent (69 out of 7398) were children.(1) In contrast, in the African region 14.5 percent (2 822 out of 19 384) new patients had G2D, six percent of which were children.(1)

The human immunodeficiency virus (HIV) with leprosy co-infection has been sparsely reported in the literature. The conclusion emanating from the reported patients is that HIV affects patients with leprosy minimally even though the HIV rates are high in leprosy endemic areas.(27) *M. leprae*, unlike *Mycobacterium tuberculosis* and *Mycobacterium avium complex*, does not increase HIV susceptibility.(27) Paradoxically, the HIV-leprosy co-infection does not affect the spectrum of leprosy.(27) Even though the HIV affects host cell mediated immunity, its co-infection with leprosy does not lead to shift to the lepromatous pole.(27) The treatment response is not affected by the co-infection. The leprosy reactions are more frequent in patients co-infected with HIV and rapid phase immune reconstitution seen with initiation of HIV treatment allows for the manifestation of pre-existing leprosy.(27)

1.6. Treatment and outcome

Treatment goals in leprosy have shifted over decades as the search for cure was sought.(28) The announcement of the 1991 WHO leprosy elimination targets was followed by a six year dramatic decrease in incidence globally.(5, 28) The MDT regimen in leprosy includes twelve months of

rifampicin 600mg monthly, dapsone 100mg daily and clofazimine 300 mg monthly then 50mg daily for adult MB leprosy patients as recommended by the WHO.(6, 29) The PB leprosy MDT regimen includes rifampicin 600mg monthly and dapsone 100mg daily for six months.(6) Adequate adherence to treatment is considered to be completion of two thirds of the recommended treatment.(29) While most centres worldwide have adopted MDT as recommended by the WHO, daily rifampicin has also been added to this treatment. In a retrospective review, Dacso *et al.* showed that their protocol using daily rifampicin in MB treatment for 2 years was superior to the use of monthly rifampicin.(7) Of the 55 patients with MB leprosy who received three drugs including daily rifampicin, no relapses were found after 10 to 15 years follow-up.(7)

Cure is a difficult term to define in the setting of leprosy treatment. Kaur *et al*. defined clinical cure as disappearance of erythema and induration of skin lesions, and non-tender nerves with no increase in size of the lesions.(29) In another study a patient was simply considered cured once an adequate fixed duration multidrug course was completed.(30) Kaur *et al.* reported cure rates of 64 percent (12 out of 28 PB patients and 52 out of 72 MB patients) after the use of fixed duration MDT as recommended by the WHO.(29) The definition of cure in the leprosy setting should include microbiological cure. The neurological sequelae of the disease and their complications often remain, even in patients where microbiological cure is demonstrated.

Relapses following leprosy MDT are uncommon. The diagnosis of relapse may be suspected based on clinical, bacteriological, therapeutic or histological criteria.(31) A relapse may be suspected if the size of lesions increases, new lesions appear, or erythema and infiltration reappear after subsiding.(31) This may be accompanied by positivity in bacilloscopy when smears were negative at two examinations during surveillance period, or an increase of BI by 2+

in two sites at two examinations, provided the patient has taken two-thirds of the MDT recommended by the WHO.(31)

Differentiating an upgrading reaction from a relapse may be difficult. An upgrading reaction should respond to prednisolone treatment.(31) Histological a relapse will show the reappearance of granuloma in PB patients and increased infiltration of macrophages with intact bacilli in MB patients.(31) Relapse rates range from zero to twenty percent.(7, 9, 32)

Drug resistance may be the cause for relapse.(31) Mouse foot-pad studies can be used to confirm resistance, however, this testing method is not available in many centres globally.(31) It is very difficult to compare relapse rates among various studies due to different relapse definitions and varying follow-up durations.(7)

Dacso *et al.* reported a relapse rate of 0.8 percent when follow-up duration was between ten to fifteen years and most patients received daily rifampicin and an extended duration of treatment for one year for PB and two years for MB (7). Overall, reported relapse rates have varied from zero to twenty percent at two years follow-up after MDT. (7) Guerrero-Guerrero *et al.* reported a relapse rate as high as 20 percent (33 out of 165) among MB patients. Similarly, a retrospective study of 3248 patients by Ali *et al* reported relapse rates of 0.84 percent for MB and 1.9 percent for PB.(32)

Despite global efforts to completely eliminate leprosy, it continues to spread in South Africa causing recognisable morbidity. South African literature has very scanty information regarding the current leprosy situation. Studying leprosy patterns at Chris Hani Baragwanath Academic Hospital (CHBAH), which is the largest hospital in SA, will pave the way in further understanding the situation in the country regarding this infection.

1.7. Study aims and objectives

1.7.1. Aims

The aim of the study is to examine the leprosy patterns at CHBAH and to ascertain if our recent trends, demographics, disease spectrum and treatment outcomes are parallel with global patterns as well as in line with the current WHO strategy of reducing the disease burden further by 2020.

1.7.2. Objectives

1. To describe the trend of new leprosy patients at CHBAH from 1999 to 2015.
2. To determine the demographics of patients treated for leprosy at CHBAH during this period.
3. To describe the clinical spectrum of leprosy in patients treated at CHBAH during this period.
4. To determine the treatment outcomes of patients treated for leprosy during this period.

1.8. Method

1.8.1. Study design

This is a retrospective, descriptive study of patients diagnosed and treated with leprosy at CHBAH from 1st January 1999 to 31 December 2015. Data will be obtained from clinical records of all patients diagnosed with leprosy at this hospital. The diagnosis of leprosy is based on clinical examination, histopathological findings and slit-skin smears results. The clinical examinations will be carried out by medical doctors at the dermatology clinic in the hospital. The skin smears will be stained by Ziehl-Neelsen methods for acid fast bacilli. The histopathological findings will be obtained from skin biopsy reports analyzed by the Department of Pathology at the National Health Laboratory Services.

1.8.2. Study population inclusion criteria

Clinical records will be reviewed to include all adults and children who have had a definite diagnosis of leprosy, and are treated and followed up for leprosy.

1.8.3. Site of the study

The CHBAH is a tertiary level public hospital in Soweto, Johannesburg, SA.(33) It is a teaching hospital for the medical school at the University of Witwatersrand.(33) Johannesburg is the largest city in SA with population of 4,4 million in 2016.(34) The hospital serves as a tertiary centre for a number of hospitals falling under its catchment area.(33) It is a designated referral treatment centre for leprosy patients in Johannesburg. The hospital is the third largest in the world with 3200 beds.(33) The population in Johannesburg is diverse including immigrants from various parts of Africa and other parts of the world.(34)

1.9. Study definitions

1.9.1. Trend

Trend refers to the pattern of increases or decreases in the number of new leprosy patients annually during the study period.(8)

1.9.2. Demographics

Demographics will include age at diagnosis, gender, country of origin and the history of contact.

1.9.3. Clinical spectrum

The clinical spectrum of leprosy will include the classification, leprosy reactions, neurological involvement as well as association with HIV infection.

Patients will be divided according to the WHO operational classification where patients are categorized according to the number of lesions, PB if the number of lesions is five or less, and MB if there are more than five skin lesions.(20)

Patients will also be categorized according to the RJC based on immunological and histological aspects into TT, BT, BB, BL and LL.(20) The patients' classifications will be determined with the help of clinical assessment, biopsies and skin slit smear results which were done prior to treatment initiation and during the follow-up period and recorded in their clinical records.(20)

BI is the result of bacilloscopy of slit-skin smears according to the Ridley logarithmic scale from 1+ to 6+, while morphological index (MI) is the presentation of *M. Leprae* as intact, fragmented, or granular.(3) Only intact bacilli are viable.(20) Both BI and MI are used together with histopathological findings to place patients in one of the five subtypes in the RJC.(20)

Indeterminate leprosy is defined as the initial stage of leprosy characterized by single or multiple hypopigmented macules with no erythema or infiltration. There is no associated peripheral nerve thickening with negative skin slit smears and nonspecific findings on histopathology.(3)

A type 1 reaction is diagnosed when rapid swelling and erythema of existing skin lesions is noted.(22) If it is associated with increasing cell mediated immunity, a rapid decrease in the number of bacilli as seen within the first few months of MDT. It is known as a reversal or upgrading reaction.

A type 1 reaction is referred to as a downgrading reaction if it occurs in an untreated patient due to rapid increase of bacilli.(21) Painful erythematous nodules or pustules are present on the extensors of the limbs, together with glomerulonephritis, iridocyclitis, orchitis or dactylitis.(21) Histologically it is a neutrophilic leukocytoclastic vasculitis.(21)

Neurological involvement is represented by disability grade.(26) For peripheral nerve involvement, grade 0 represents no functional impairment, grade 1 corresponds to anaesthesia of hands or feet with no visible deformity, and grade 2 is presence of both anaesthesia and visible deformities which are trophic ulcers, claw deformities and bone resorption of the extremities.(26) For the eyes, grade 0 is no vision loss related to leprosy, grade 1 is some visual impairment (vision 6/60 or better), and grade 2 is severe loss of vision.(26)

1.9.4. Treatment outcome variables

The considered treatment outcome variables are treatment completed, patient cured, transferred, relapsed, died or defaulted.(35) The treatment is deemed completed if the PB patient completes WHO recommended six months of rifampicin and dapsone within a nine month period, and in

MB patients one year of MDT with rifampicin, dapsone and clofazimine is completed within 18 months.(6, 29)

Relapse is defined as the appearance of one or more new lesions or an increase in size of the lesion, and erythema or swelling where it had subsided as detected by a clinician.(31) This is accompanied by either histological or bacteriological confirmation or both. Histologically, a relapse is represented by the reappearance of granulomas in PB patients or an increased infiltration of macrophages with solid staining bacilli in MB.(31) Bacteriological confirmation includes positivity in skin slit smears in a patient where smear negativity had been achieved, or a 2+ increase in BI following successful treatment.(31) The results range from 0 to 6+ on the semi- logarithmic scale, and it falls about one point per year with effective treatment as the dead bacilli are absorbed.(31) Relapse will be assessed at clinical examinations done every six months up to 18 months for PB and up to 24 months for MB, which constitute a period one year follow-up post treatment. Patients will be considered defaulters if they do not take their medication for more than three months for PB infection or six months for MB infection. Retreatment is given to defaulters who return subsequently.(31)

Cure is defined as complete disappearance of the skin lesion(s) in BI negative paucibacillary patients.(29) In MB types, BI negativity is a measure of cure. Cure will be assessed at clinical examinations carried out every six months up to one year after the treatment period according to the WHO is completed. This is 18 months for PB and 24 months for MB.

Patients who are sent to complete their medication in other districts or provinces are considered transferred. Death will be a treatment outcome for those who lose their lives during the treatment

period, including the one year follow-up period. This includes a total of 18 months duration for PB and 24 months duration for MB.

1.10. Data analysis

Data will be extracted from paper file records which are stored at the dermatology clinic at CHBAH. The number of leprosy patients will be reported as frequencies or percentages. A line graph will be used to show the trend in numbers of leprosy patients over time in years. Means and standard deviations will be used for continuous variables such as age. Medians and interquartile ranges will be used if the data are not normally distributed. For categorical variables such as age category, gender, country of origin, history of contact, classification, leprosy reactions, neurological involvement, association with HIV, and treatment outcomes, frequencies and percentages will be reported.

Graphical demonstration to display the results visually will be done using pie charts or bar charts. Bivariate analysis will be used to determine if there are any differences in proportions of these variables by the WHO and Ridley Jopling classifications. Chi-square tests will be used to ascertain associations between the categorical variables if its assumptions are satisfied, and if not, the Fischer exact test will be used.

1.11. Limitations

This is a retrospective study and therefore bias in reporting cannot be completely excluded. Some data may be missing too because of the time that has lapsed. Selection bias cannot be ruled out as patients presenting to CHBAH, a tertiary hospital, represent a highly selected population.

1.12. Ethics

Permission to conduct the study will be obtained from the Chief Executive Officer of CHBAH and the Department of Internal Medicine. Ethics clearance will be obtained from Human Research Ethics Committee (HREC) of the University of Witwatersrand. The confidentiality of subjects will be maintained at all times and data will be presented in an anonymized format so that participants are not identifiable.

1.13. Finance

This will be a self-funded study with the following costs

Item	**Cost**
Software	R650
Printing	R1000
Paper	R800
Total	**R2450**

1.14. Schedule

	Mar-May 2018	June - Dec 2018	Feb-June 2019	July-Sept 2019	Sept-Dec 2019	Jan-Mar 2020
Research protocol						
Protocol assessment and ethics application						
Data collection						
Data analysis						
Writing Up						

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CHAPTER 2: SUBMISSIBLE ARTICLE

Title:

The patterns of leprosy at Chris Hani Baragwanath Academic Hospital

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Conflict of Interest: None

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Word count: 4354

Abstract word count: 393

Abstract

Background

The World Health Organization announced a strategy to eliminate childhood leprosy infections, visible deformities and discriminatory legislation against leprosy patients by 2020. However challenges in achieving leprosy-free world and preventing neurological sequelae still exist. Human immunodeficiency virus (HIV) infection has been a challenging burden in our population. HIV-leprosy co-infection may result in an increase in frequency of leprosy reactions without affecting the spectrum of leprosy. From 1921 to 1997 the leprosy prevalence remained less than one patient per 10 000 population. Current South African literature has very scanty information regarding the leprosy infections.

Objectives

The purpose of this study was to describe the trend of new leprosy patients from 1999 to 2015, including the demographics, clinical spectrum and treatment outcomes of patients treated for leprosy at Chris Hani Baragwanath Academic Hospital (CHBAH) during this period.

Method

A retrospective review of patients' clinical records was undertaken. Data on demographics, clinical spectrum including the leprosy classification, reactions, neurological involvement, HIV infection association as well as treatment outcomes were extracted. Data analysis was performed using descriptive and inferential statistics and a time series analysis.

Results

An upward trend from 1999 to 2001 was followed by a decline in the number of new patients. Eighty patients were registered over a period of 17 years, with a male-to-female ratio of 3:1. Thirty six patients were immigrants. Five were children less than 15 years old. Multibacillary leprosy was the most common type with 71 patients. Thirty six patients were lepromatous leprosy subtype, 22 were borderline-lepromatous, 13 were borderline-tuberculoid, six were midborderline and three were tuberculoid leprosy. Thirty one patients presented with reactions, type 1 in nine patients and type 2 in 21 patients, with both types in one patient. Grade 2 neurological deformities were diagnosed in 37 patients, of which two were children. Eight patients were found to have HIV-leprosy co-infection. Out of 52 patients who completed treatment, 26 were cured and 26 were lost to follow-up. Twenty-one patients defaulted treatment while three patients relapsed.

Conclusion

This study highlights the current status of leprosy in a low endemic centre with declining numbers of new patients. Multibacillary forms with grade 2 disabilities are common. The constant emergence of leprosy in our population highlights shortfalls in our control campaigns. Furthermore, a high rate of grade 2 disabilities necessitates scrutiny of education directed at early patient detection and follow-up strategies.

Introduction

Leprosy, caused by *Mycobacterium leprae (M. leprae)* infection, has been the focus of an elimination campaign worldwide.(1) In an attempt to reduce the disease burden further, the World Health Organization (WHO) in 2016 committed to a strategy to achieve a world free of leprosy.(1) In 2015, the highest incidence of the disease was found in India, Brazil and Indonesia, together accounting for 81 percent of new patients.(2) From 2015-2016 Africa contributed about nine percent to leprosy incidence.(1) Risk factors of leprosy in endemic countries are low socioeconomic status, poor education, contact with leprosy and genetic factors. These may influence endemicity, however they do not fully explain the differences in endemicity that exists between African and Asian regions.(2)

In terms of demographics, the middle-age presentation in leprosy is a common finding.(3-5) The proportion of children below the age of 15 years has varied in different studies, ranging from 1.9 percent (90 out of 4770) to 18 percent (13 out of 74).(6, 7) Males have consistently been the majority of patients, both in high and low endemic centres.(3, 6, 8) This has been attributed to male migration patterns.(6) In a systematic review by Price *et al*. which extracted data from multiple countries, infections in females were noted to be detected late.(9)

A close prolonged contact with an infected patient increases the risk by five to eight times.(4, 10) Richardus *et al.* found that a higher percentage (62%) of new leprosy patients had a history of leprosy contact in a low endemic area compared to a high endemic area (25%).(8) Foreign-born patients (862 out of 32 673) were reported in 30 countries in 2017. (11) All new leprosy patients in Qatar and the United Arab Emirates being foreign-born.(1)

Multibacillary leprosy (MB) corresponds to lepromatous and borderline forms.(7). Overall, MB forms predominate globally, with 59.1 percent (127,013 out of 214,783) in 2016 and 60.2 percent (126,783 out of 210,758) in 2015 being new leprosy patients globally.(1, 12) In some cases, paucibacillary leprosy (PB) forms the majority in high endemic areas.(6-8)

Neurological involvement occurs in all forms of leprosy. It is often early and asymmetrical in tuberculoid leprosy (TT), compared to late and symmetrical in lepromatous leprosy (LL).(2, 13) Severity of neurological involvement is represented in a disability grade. Grade 1 is the presence of anaesthesia, while additional visible deformities are present in grade 2.(14) In 2016 the proportion of new patients with grade 2 disabilities (G2D) in the high endemic South East Asia region was 4.6 percent (7398 out of 161 263), and 0.9 percent (69 out of 7398) of them were children.(1) In contrast, in the African region 14.5 percent (2822 out of 19384) new patients had G2D, six percent of which were children.(1)

Type 1 reactions, which include downgrading and upgrading reactions, are common in immunologically unstable borderline subtypes, namely midborderline leprosy (BB), borderline-tuberculoid leprosy (BT) and borderline-lepromatous (BL) leprosy.(15, 16) Type 2 reactions, also known as erythema nodosum leprosum (ENL), are commonly found in lepromatous subtypes with high bacillary load.(15) In a study where borderline subtypes predominated, Chhabra *et al.* reported that more patients presented with type 1 reactions (258 out of 849) compared to type 2 (60 out of 849).(5) In a review, Kahawita *et al.* demonstrated a varying type 1 reaction prevalence rate ranging from 19 to 29 percent. (16)

It has been reported that the human immunodeficiency virus (HIV) affects patients with leprosy minimally even though the HIV rates are high in leprosy endemic areas.(13) *M. leprae*, unlike

Mycobacterium tuberculosis and *Mycobacterium avium complex*, does not increase HIV susceptibility.(13) The leprosy reactions are more frequent in patients co-infected with HIV and the rapid phase immune reconstitution seen with the initiation of HIV treatment allows for manifestations of pre-existing leprosy.(13, 17)

The multidrug treatment (MDT) regimen in leprosy includes a combination of rifampicin, dapsone and clofazimine for twelve months in MB leprosy and for six months in PB leprosy, as recommended by the WHO.(18, 19) The commonly considered treatment outcome variables are treatment completion, defaulting, cure, relapse and death.(20) Cure rates of 64 to 100 percent have been reported in various studies.(3, 18) Reported relapse rates have varied from zero to twenty percent following MDT.(21-24) Detection of relapses has been more likely with follow-up of between 3.5 to 6 years, and higher bacillary loads.(21, 23)

Understanding of the current situation of leprosy in our setting relies on documented information in the literature. This information is currently scarce in South Africa (SA). Furthermore, despite global efforts to eliminate leprosy, it continues to spread in South Africa causing recognisable morbidity. Therefore studying leprosy patterns at Chris Hani Baragwanath Academic Hospital (CHBAH), which is the largest hospital in SA, will assist efforts to understand its patterns in the country.(25)

Objectives

The purpose of this study is to describe the current leprosy trends, demographics and disease spectrum, and to determine the treatment outcomes of patients treated for the disease at CHBAH from 1999 to 2015.

Method

Study sample

We retrospectively reviewed clinical records of 80 adult and pediatric patients diagnosed and treated with leprosy at CHBAH from 1 January 1999 to 31 December 2015. The hospital is a designated referral treatment centre for leprosy patients in Johannesburg, the largest city in SA. The population of Johannesburg is diverse including immigrants from various parts of Africa and other parts of the world. For the purposes of data analysis patients who were younger than 15 years were classified as children.

Data collection instrument

The data collection instrument was a data sheet designed to collect the necessary information. The diagnosis of leprosy was based on clinical examination, histopathological findings or slit-skin smears results. The demographic data obtained from recorded information included age at diagnosis, gender, region of origin, history of leprosy contact. Using the United Nations Sub-Saharan African divisions and the world map, the region of origin was divided into Northern, Central, Eastern, Western and Southern Africa, and Asia or other, based on where the patients were born. The Southern Africa region was further divided into member countries and SA was divided into provinces. The trend was formulated using the total number of new leprosy patients over the years. The patients who were relapses admitted to our centre for retreatments were excluded in formulation of trend of new cases, otherwise included for demographics, clinical spectrum and treatment outcome analysis.

The clinical examinations were carried out by a doctor who is a consultant or a senior registrar in dermatology at the institution. The skin-slit smears were done by a qualified technician and stained by Ziehl-Neelsen methods for acid fast bacilli. The histopathological findings were

obtained from skin biopsy reports found in clinical records analyzed and reported by the Department of Pathology at the South African National Health Laboratory Services. HIV positive status was confirmed on antibody or antigen (Rapid or Elisa) tests. Initial cluster of differentiation 4 (CD4) counts in cells/μL at the time of presentation were used. The information on the clinical spectrum of leprosy which included the leprosy classification, leprosy reactions, neurological involvement as well as association with HIV infection was extracted from the clinical records.

Records were classified into WHO categories, PB if the number of skin lesions was five or less and MB if they were more than five.(26) In addition, a record was classified into one of the Ridley and Jopling classification (RJC) variants i.e. TT, BT, BB, BL and LL using a combination of clinical assessment, skin slit smear results and histopathological findings.(26)

Information on the leprosy reactions the patient presented with during the course of follow-up period was captured. A type 1 reaction was diagnosed when rapid swelling and erythema of existing skin lesions was noted.(15) Type 1 reactions were classified as downgrading if occurring in untreated patients as borderline disease shifts towards lepromatous pole, and upgrading if occurring with antibiotic treatment.(27) A type 2 reaction was diagnosed if a patient presented with new painful erythematous nodule, with a neutrophilic leukocytoclastic vasculitis histopathology or other organ involvement in form of arthritis, neuritis, glomerulonephritis, iridocyclitis, orchitis and dactylitis. (28)

Neurological involvement information as obtained from the records was represented by disability grade.(14) For peripheral nerves involvement, grade 0 represented no functional impairment; grade 1 corresponded to anaesthesia of hands or feet with no visible deformity while grade 2 was

presence of both anaesthesia and visible deformities such as trophic ulcers, claw deformities and bone resorption of the extremities.(14) For the eyes, grade 0 was no vision loss related to leprosy, grade 1 was some visual impairment (vision 6/60 or better), and grade 2 was severe loss of vision.(14)

The considered treatment outcome variables were treatment completed, patient cured, transferred, relapse, died or defaulted. The treatment was deemed completed if the PB patient completes WHO recommended six months of rifampicin and dapsone within a nine month period, and in MB patients one year of MDT with rifampicin, dapsone and clofazimine was completed within 18 months.(18, 19, 29)

Cure was defined as complete disappearance of the skin lesion(s) in bacillary index (BI) negative paucibacillary patients. In MB types, BI negativity was a measure of cure.(18)

Relapse was defined as appearance of new lesion (s) or increase in size of the lesion, erythema or swelling where it had subsided detected by a clinician.(23) This was confirmed histologically by reappearance of granulomas in PB patients and as increased infiltration of macrophages with solid staining bacilli in MB or 2+ increase in BI following successful treatment. (23)

Cure and relapse were assessed at clinical examinations done every 6 months up to 18 months for PB and up to 24 months for MB, which constituted a period of one year follow-up post treatment.

Patients were considered defaulters if they did not take their medication for more than 3 months for (PB infection) or 6 months for (MB infection).(29) Retreatment was given to defaulters who subsequently returned.(29) Patients who were sent to complete their medication in other

hospitals were considered transferred. Death was the treatment outcome for those who lost their lives during the treatment period including the one year follow-up period, a total of 18 months duration for PB and 24 months duration for MB.

Statistical analysis

Data analysis and interpretation was conducted using both descriptive and inferential statistics. Descriptive statistics were used to describe the distribution of the data using measures such as mean, standard deviations, minimum and maximum for numerical variables such as age while frequencies and graphs were used to report categorical variables. The number of leprosy patients was reported as frequencies or percentages. A line graph was used to show the trend in numbers of leprosy patients over time.

For categorical variables such as age category, gender, country of origin, history of contact, classification, leprosy reactions, neurological involvement, association with HIV and treatment outcome, frequencies and percentages were reported. Graphical demonstration to visually display the results was done using pie charts or bar charts. Inferential statistics were used to make judgments based on the sample data collected. The chi square test was used to ascertain associations between the categorical variables if its assumptions are satisfied, otherwise the Fischer exact test was used. The Chi square test was used to test for association between RJC and leprosy reaction as well as HIV status and leprosy reaction.

Ethical clearance

Anonymized data was used, with patients' identity protected, and all collected data was secured. Permission for analysis and publication was obtained from Human Research Ethics Committee (HREC) of the University of Witwatersrand.

Results

Demographic characteristics

A total of 80 leprosy patient records were reviewed in the study. The majority (70) reflected new patients while 10 (12.5%) were relapses after MDT. The sociodemographic features of all patients are summarized in Table 1. There was a preponderance of males (76.2%) with a male-to-female ratio of 3:1.

Table 1: Baseline demographics

Demographic (N=80)	Description	N (%)
Entry status	New patients	70(87.5%)
	Relapse after MDT	10(12.5%)
Gender	Female	19(23.8%)
	Male	61(76.2%)
Age group in years	Less than 15	5(6.2%)
	15-30	29(36.2%)
	31-45	26(32.5%)
	46-60	14(17.5%)
	61-75	6(7.5%)
Region of origin	Asia	6(7.5%)
	Central Africa	5(6.2%)
	Eastern Africa	8(10.0%)
	Southern Africa	59(73.8%)
	Western Africa	2(2.5%)
Contact history	No	56(70%)
	Yes	24(30%)

N: number; MDT: multidrug treatment

As shown on Figure 1, only five (6.2%) patients were children less than 15 years of age. The minimum and maximum age of the participants was four and 73 years respectively, with the mean (±SD) age of 36±15.27 years.

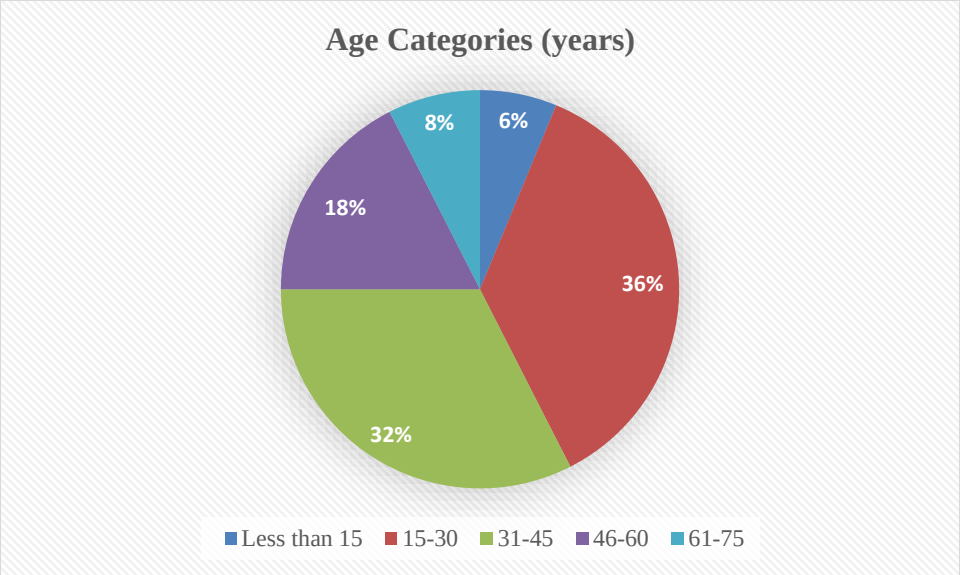

Figure 1: Age categories

The majority of patients, 59 (73.8%) were from the Southern African region with only two (2.5%) from Western Africa as shown in Figure 2. A total of 56 (70%) of the participants did not have any history of contact with a leprosy patient while 24 (30%) reported to have had contact as shown in Table 1.

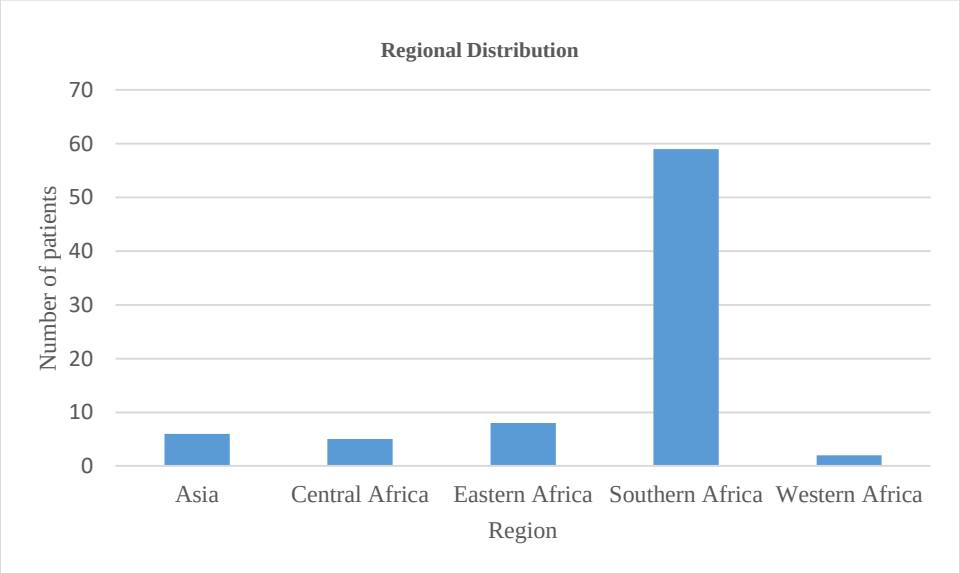

Figure 2: Region of origin of the patients

Figure 3 shows the number of leprosy patients divided according to Southern African regions they are from. South African-born patients recorded the highest number of leprosy patients compared to migrants groups.

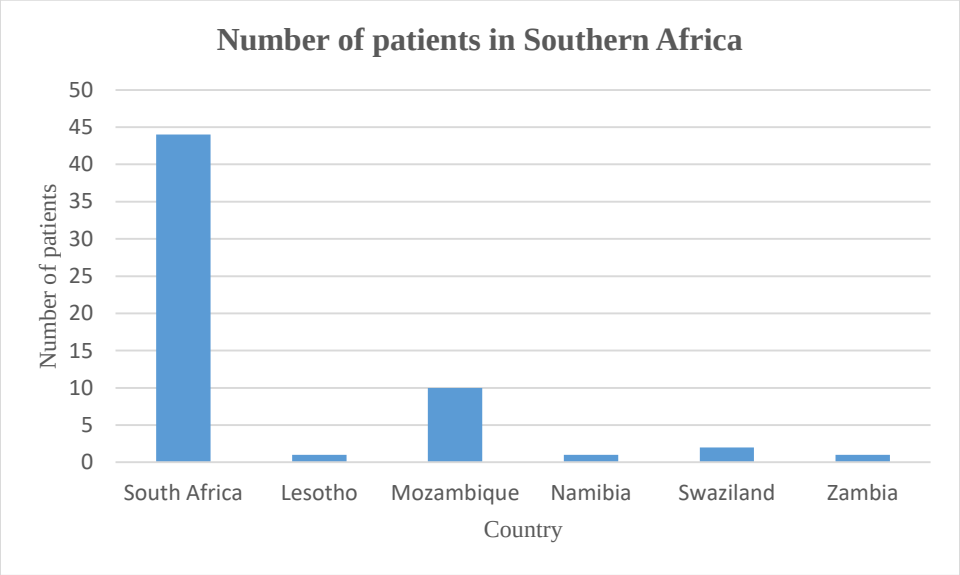

Figure 3: Number of patients from the Southern African region

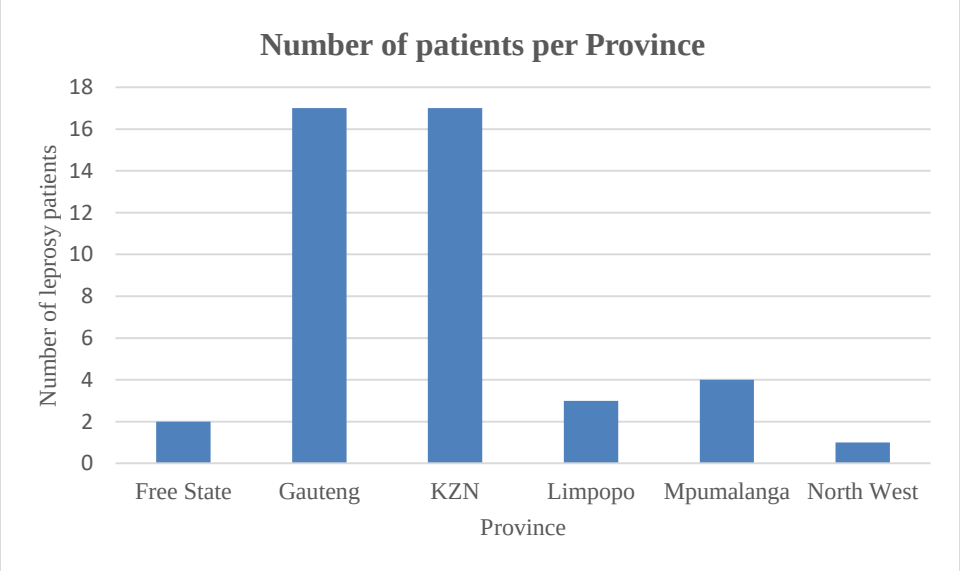

Figure 4: Province of origin for South African patients

KZN: KwaZulu-Natal

The number of leprosy patients divided according to South African provinces is shown in Figure 4. Among 44 South African-born patients, the highest numbers were originally from Gauteng and KwaZulu-Natal with 17 patients each.

Trend

The number of new leprosy patients showed a decline since 2001 as shown in Figure 5. Before this period, from 1999 to 2001, an upward trend was recorded. Since 2004 the number of new patients stabilized with very little change until 2015.

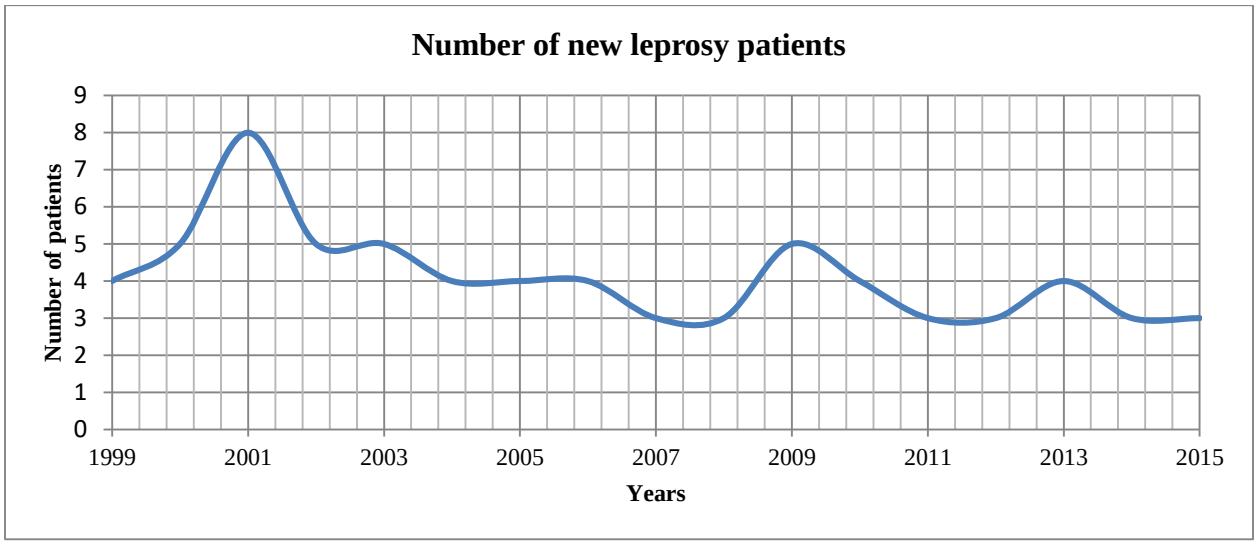

Figure 5: Trend of new leprosy patients (1999-2015)

Clinical spectrum

Classification

As shown on Table 2, 71(88.8%) were MB and nine (11.2%) were PB. According to RJC the majority, 36 (45.0%), were classified as LL as shown in Figure 6.

Table 2: Clinical spectrum

Clinical spectrum (N=80)	Description	N (%)
WHO classification	MB	71(88.8%)
	PB	9(11.2%)
Leprosy reaction	Type 1	9(12%)
	Type 2	21(28%)
	None	44(58.7%)
	Both Type 1 and type 2	1(1.3%)
Leprosy reaction	Upgrading/Reversal	9(29.0%)
	ENL	21(67.7%)
	ENL and upgrading	1(3.3%)
Neurological disability	Grade 0	19(23.8%)
	Grade 1	24(30.0%)
	Grade 2	37(46.2%)
HIV status	Negative	23(28.7%)
	Not done	49(61.3%)
	Positive	8(10%)
CD4 count in cells/µL	>200	6(7.5%)
	101-200	1(1.2%)
	Not done	73(91.3%)

N: number; WHO: World Health Organization; HIV: Human Immunodeficiency Virus; CD4: Cluster of differentiation 4; MB: multibacillary; PB: paucibacillary; ENL: erythema nodosum leprosum

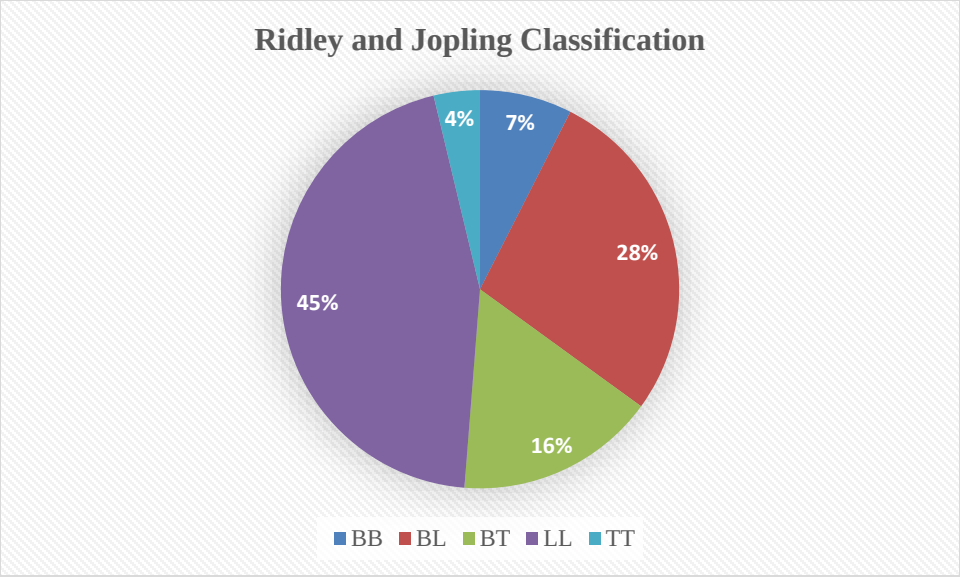

Figure 6: Proportion of patients in Ridley and Jopling classification

BB: midbordeline leprosy; BL: borderline lepromatous leprosy; BT: borderline tuberculoid leprosy; LL lepromatous leprosy; TT: tuberculoid leprosy

Leprosy reactions

Nine (12%) patients had type 1 leprosy reaction, 21(28%) had Type 2, one (1.3%) had both type 1 and 2 reactions, and 44(58.7%) had no reactions. All the patients who had type 1 reaction had an upgrading reaction, as shown in Table 2. Of the patients with ENL, 17 had the LL variant while four had the BL variant. The upgrading reaction was found among LL (one), BL (four), BB (one) and BT (three).One patient with BL had both ENL and upgrading reactions as shown in Table 3.

Table 3: Leprosy reactions and neurological disability

RJC	Leprosy reactions				Neurological disability		
	ENL	Upgrading	ENL and Upgrading	None	Grade 0	Grade 1	Grade 2
LL	17	1	0	18	10	9	17
BL	4	4	1	13	5	8	9
BB	0	1	0	5	1	1	4
BT	0	3	0	10	1	6	6
TT	0	0	0	3	2	0	1

RJC: Ridley and Jopling Classification; LL: lepromatous leprosy; BB: midbordeline leprosy; BT: borderline tuberculoid leprosy; TT tuberculoid leprosy; ENL: erythema nodosum leprosum

Neurological involvement

From the available data, 24 (30.0%) had grade 1 neurological disability, 37(46.2%) had grade 2 and 19 (23.8%) had none as shown in Table 2. Of the five children under 15 years, three had grade 0 while two had G2D. Patients in the LL variant formed the majority (26) of those with neurological disability variant 17 of which have G2D as shown in Table 3.

Association with HIV

There were 23(28.7%) patients who tested negative for HIV, 8(10.0%) tested positive while in 49 (61.3%) HIV testing was not done as shown in Table 2. Of the eight patients with a positive HIV result, six had a CD4 count of more than 200 cells/µL and only one had a CD4 count less than 200cells/µL. The CD4 count testing was not done on the rest of the patients. Of the HIV positive patients, two had ENL compared to eight who were HIV negative, as shown in Table 4. The result of the fishers exact test indicated that there was no association between HIV status and leprosy reaction (p=0.584).

Table 4: HIV status

HIV status	Reaction			
	ENL	Upgrading	ENL and Upgrading	None
Negative	8	3	1	11
Positive	2	0	0	6
Not done	11	6	0	32

HIV: Human Immunodeficiency virus; ENL: erythema nodosum leprosum

Treatment outcomes

Fifty two patients had completed treatment and 26 (50%) were cured. In the other half cure was not documented. A total of 21(26.2%) defaulted, three (3.8%) experienced relapse while four (5.0%) were transferred, as shown in Table 5.

Table 5: Treatment outcomes

RJC	Treatment outcome				
	Completed		Defaulted	Relapsed	Transferred
	Cure not documented	Cured			
LL	15	10	11	0	0
BL	3	7	8	3	1
BB	3	1	1	0	1
BT	3	7	1	0	2
TT	2	1	0	0	0
Total N=80 (%)	**26 (32.5%)**	**26 (32.5%)**	**21 (26.2%)**	**3 (3.8%)**	**4 (5%)**

RJC: Ridley and Jopling classification; LL: lepromatous leprosy; BL: borderline lepromatous leprosy; BB: midboderline leprosy; BT: borderline tuberculoid leprosy; TT: tuberculoid leprosy; N: number

Discussion

Even though leprosy is not a major public health problem in SA, new patients continue to emerge in Johannesburg. This study reports leprosy patterns at CHBAH.

The majority of the patients in this study were male. This is consistent with global evidence (4-6, 12) Men have been reported to be more likely to migrate to cities for employment reasons which could explain their predominance. This may also be due to socioeconomic differences in favour of men, making healthcare access easier for them. The mean age of presentation was in the middle age group which is consistent with the findings of other similar studies.(3-5) This group represents the working force who are often breadwinners in families and thus of great concern. Very few patients were children (<15 years old) in line with the findings of other studies.(6, 7, 12)

Around half of patients were South African-born, with leprosy more common in patients from Gauteng and KwaZulu-Natal (KZN).This is of concern as it may indicate clusters of active infection transmission in these locations. Our centre is located in Gauteng, therefore the high proportion of patients originating from the province may be due to easier access. The presence of similarly high proportion of patients from KZN, which surpasses that of neighbouring provinces, is concerning as it may indicate the present of higher numbers of patients with active infection in the province. Further scrutiny is needed in studying these transmission areas to understand the transmission patterns and to control them. Equally, the importance of leprosy screening programmes for immigrants at country entry ports cannot be ignored as the immigrant population forms about half of the total number of our patients.

This study found more than two thirds of patients with no known history of contact to an index patient. The older the patient the less likely they were to have a known contact.(30) Richardus *et al.* found a lower proportion (one third) of new leprosy patients with no contact history in low endemic Thailand compared to high endemic Bangladesh.(8) Our study is done in SA which is a low endemic area; however proportions of patients who had no history of contact were higher. This may represent active transmission of leprosy from undiagnosed patients in our communities. Other patients may be unaware of leprosy diagnosis within their contact circles. This means that our leprosy education programmes need to be stepped up. Furthermore, the presence of foreign-born immigrants in this study may explain the lower proportions of patients with history of known contact as it may be difficult to keep track of a possible diagnosis of the contacts in patients who are constantly relocating.

An increasing trend from 1999 to 2001 was followed by declining trend noted from 2001 which stabilized in 2004 with very little change in numbers thereafter. The reason for the increasing number of leprosy patients in this period is unclear, however it may represent a period of increased influx of immigrants from leprosy endemic neighboring countries. Perhaps this period coincides with a local leprosy detection campaign resulting in detection of new patients or treatment accessibility challenges in the community. This needs further evaluation. The declining trend noted from 2001 is similar to the described worldwide patterns.(11, 31)

In our study, we identified a predominance of MB patients (88.8 %) with LL forming the majority of this group. The WHO reported that in the Democratic Republic of Congo and Ethiopia, 60 to 80 percent of new patients detected were MB forms in 2016.(1) A similar pattern of MB forms predominance has been recorded in other similar studies.(3, 4, 7) Our region is a low endemic area where MB forms are known to predominate.(7, 8) The predominance of MB

forms may be due to poor immunity against leprosy in our population. This finding raises concerns regarding transmission of the infection as these patients are known to carry a high bacillary load.

In this study, 28 percent had type 2 reactions while 12 percent had a type 1 reaction at some point during their follow-up period. Previous studies have found a varying prevalence rate of type 1 reactions ranging from 19 to 30% (5, 16). Type 1 reactions occur in borderline forms (BT, BB, and BL) which are immunologically unstable. (15, 16) Type 2 reactions develop in patients with the high bacillary loads seen in LL and BL leprosy.(15) In our study the lepromatous group (LL and BL) predominated. Therefore it is not surprising that type 2 reactions were common.

Nearly half (46.2%) of our patients had G2D, 5.4 percent of which were children. Varying proportions of patients with G2D have been reported. In a global leprosy update in 2016, the WHO reported that 14.5 percent of new leprosy patients had G2D in the African region compared to 4.6 percent in the South East Asian region. (1) Lower proportions of patients with G2D have been reported in similar studies.(3, 6) Delay in diagnosis and default in treatment are among the high risk factors for G2D.(3, 32) The high percentage of G2D in this study may indicate late presentation or delayed diagnosis in our region. Poor access to specialist dermatology services is a reality in parts of our country which may be responsible for the delay in diagnosis. Furthermore, the percentage of children presenting with G2D was higher in our study compared to comparable reports.(1, 3) This indicates active transmission in our population and poses a hindrance to achieving the WHO set goal of no children with G2D by 2020.

About a third of patients had had an HIV test. Leprosy-HIV co-infection was found in 10 percent and the majority of these had CD4 counts greater than 200 cells/µL. Case reports showed that

HIV did not appear to increase leprosy susceptibility, but co-infected patients may have had an increased number of reactions.(13) Among the HIV positive patients, a few had ENL and none had a type 1 reaction. This is in contrast with reports of frequent reactions in co-infected patients, however our numbers were small.

In the present study, 65 percent of patients completed treatment. About half of these were cured and in the remainder cure was not documented. Our cure rate was 32.5 percent which is lower than the clinical cure rate of 64 to 100 percent reported in other studies.(3, 18) Exclusion of foreign-born patients in cure rate calculations may have been responsible for higher cure rates in the Omanian study whereas in our study foreign-born patients were included in determining cure rates.(3) The loss of 32.5 percent of patients soon after treatment completion meant cured patient from this group were not recorded thus contributing to our low recorded cure rates. Cure rates were reported to continue to improve up to 18 months after completion of treatment.(20) In our study follow up period was 12 months after completion of therapy. Therefore extending the follow up period could have favourably altered our cure rate. Gaps in our follow-up strategies and patient education need to be revisited. The constant relocation of our migrant population may also have contributed to this.

Our relapse rate was 3.8 percent, all of which were MB patients. The reported relapse rates range from 0 to 20 percent.(21-24) Dacso *et al.* and Ali *et al.* showed lower relapse rate of 0.8 percent and 0.84 percent respectively in MB patients.(21, 22) Our relapse rates are comparable to rates reported in the literature. Poor patient compliance to the MDT regimen may have contributed to our relapses.

In terms of the limitations of this study, bias in reporting could not be completely excluded as this was a retrospective analysis. Selection bias could exist since our centre is a tertiary hospital. Our sample size was small. Furthermore, the number of years the foreign-born patients had been living in SA was not recorded. Our follow-up period was limited to one year after treatment completion which posed limitations in assessing treatment outcomes.

Conclusion

Our analysis of available records shows that despite decreasing numbers of leprosy patients in our centre, there are still clusters of transmission where MB forms still predominate. Furthermore, the high rate of G2D in new patients, including children, indicates late presentation. This presents a setback in reducing the disease burden further. Active patient detection strategies need to be intensified to facilitate early diagnosis and prompt treatment. The constant emergence of leprosy patients from both SA and neighboring African countries highlights shortfalls in our campaigns to achieve the leprosy-free region envisioned by the WHO for 2020. Our low cure rates and significant loss of patients to follow-up pose a hindrance in achieving a leprosy-free region. The need for further efforts aimed at improving early diagnosis and community awareness education campaigns cannot be overemphasized.

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CHAPTER 3: APPENDICES

3.1. Ethics clearance

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

R14/49 Dr Lindinkululeko Nkehli

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M180951

NAME: (Principal Investigator)	Dr Lindinkululeko Nkehli
DEPARTMENT:	Dermatology Chris Hani Baragwanath Academic Hospital
PROJECT TITLE:	The patterns of leprosy at Chris Hani Baragwanath Academic Hospital
DATE CONSIDERED:	28/09/2018
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Prof Colin Menezes
APPROVED BY:	Dr C Penny, Chairperson, HREC (Medical)
DATE OF APPROVAL:	13/11/2018

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary in Room 301, Third floor, Faculty of Health Sciences, Phillip Tobias Building, 29 Princess of Wales Terrace, Parktown, 2193, University of the Witwatersrand. I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit the application to the Committee. **I agree to submit a yearly progress report**. The date for annual re-certification will be one year after the date of convened meeting where the study was initially reviewed. In this case, the study was initially reviewed September and will therefore be due in the month of September each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

Principal Investigator Signature _____ Date _____

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

3.2. Data collection sheet

Data Collection Sheet

Study Title: The patterns of leprosy at Chris Hani Baragwanath Academic Hospital

Study number

Pseudonumber

Year of diagnosis YYYY

	Yes	No
New case		
Relapse after MDT		
Relapse after DDS		

Age (years) ☐

Gender

Male	Female

Country of origin

REGION	Yes	No	Specify
Northern Africa			
Western Africa			
Eastern Africa			
Central Africa			
Southern Africa			
Asia			
Other			

History of contact

Yes	No

Leprosy classification

Indeterminate leprosy

Yes	No

WHO functional group

PB	MB

Initial bacilloscopy

BI

Not done	Neg	1+	2+	3+	4+	5+	6+

MI

Not done	Neg	Intact	Fragmented	Granular

Initial histopathology

Not done	Foamy macrophages	Granulomas	Mixed

Ridley Jopling classification

LL	BL	BB	BT	TT

Leprosy reactions

None	Type 1		Type 2
	Downgrading	Upgrading/Reversal	Erythema nodosum leprosum

Neurological involvement

Disability	Grade 0	Grade 1	Grade 2	Specify
Peripheral nerves				
Eyes				

HIV	positive	negative	not done

Absolute CD4 Count (cells/uL)	Not done	<50	50-100	101-200	>200

Treatment and outcomes

Treatment	Yes	No	No. of months
DDS +daily rifampicin			
DDS + daily rifampicin+ clofazimine			
DDS+ monthly rifampicin+ clofazimine			
Alternative treatment – Specify			

Treatment Outcome	Yes	No
Completed		
Cured		
Defaulted		
Relapsed		
Transferred		
Died		