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Epidemiological and Clinical Features of Leprosy Reactions and Associated Risk Factors in Malagasy People from 2012 to 2021

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Abstract: *Introduction*: Leprosy is a transmissible infectious disease while cutaneous and neurological manifestations vary according to the patient's immunity. It is a chronic disease with acute immunological complication called leprosy reactions. Leprosy remains endemic in Madagascar. The objective of this study is to characterize the epidemiological and clinical profile of leprosy and leprosy reactions and to determine the risk factors for leprosy reactions. *Methods*: This was a retrospective, case-control study over a period of 10 years from January 2012 to December 2021 conducted among leprosy patients of the University Hospital Joseph Raseta Befelatanana. Univariate and multivariate logistic regression was used to determine the risk factors for leprosy reactions. *Results:* Of the 161 patients selected, 53 patients had a leprosy reaction. There were 91 males and 70 females with a mean age of 35.8 years (±15,47). The borderline lepromatous type was the most common clinical form. The prevalence of lepromatous reaction was 33%. Type 1 and type 2 reactions were found in 41.50% and 45.28% of cases respectively. The average time to develop leprosy reactions after the initiation of multidrug therapy was 5.80 months (±3.91). From multivariate analysis, the risk factors identified were: male gender [OR=2.64 (95% CI: 1.80-9.57), p=0.02], positive BI [OR=3.53 (95% CI: 2.41-48.98), p=0.02], MB treatment regimen [OR=8.87 (95% CI: 1.23-3.57), p=0.008)], and poor adherence to treatment [OR=1.97 (95% CI: 1.34-12.95), p=0.0354]. *Conclusion:* The knowledge of these risk factors allows for early diagnosis and treatment of leprosy reactions to prevent the morbidities due to leprae disease such as amputations and disabilities that are a source of stigma.

Keywords: Epidemiology, Leprosy, Leprosy Reaction, Madagascar, Risk Factors

1. Introduction

Leprosy also known as Hansen's disease is a chronic granulomatous disease caused by *Mycobacterium leprae (M. leprae)* or Hansen's bacillus which mainly affects the skin, peripheral nerves, mucous membranes of the upper respiratory

tract and eyes [1-3]. It is one of the neglected tropical diseases [4]. Depending on the infected individual's cellular immunity, the clinical forms of leprosy vary between two extremes: the tuberculoid form characterized by a granulomatous inflammatory reaction and the bacillus-rich lepromatous form [5].

Leprosy is an old disease that continues to be an important public health problem in several developing countries. In Madagascar, leprosy remains endemic even though the number of new leprosy cases has decreased with 1 283 cases recorded in 2019 (compared to 1 424 cases in 2018) [6]. The introduction of the multidrug therapy (MDT) by the World Health Organization in 1981 led to a decrease in the prevalence of leprosy worldwide but unfortunately the frequency of leprosy reactions increased inversely due to the bactericidal action of MDT which resulted the release of antigen stimulating an immune reaction [7, 8].

Leprosy reactions are common complications occurring in 30-50% of leprosy cases [9]. They are characterized by acute inflammatory events that may occur over the course of leprosy disease, either before, during or even years after leprosy treatment [10]. These are serious complications considered as a medical emergency responsible for amputations and neurological sequelae most often irreversible due to nerve damage following an immunological process [11]. Etiopathogenesis of leprosy reactions remains obscure. There are two main types of leprosy reactions. The type 1 reaction or reverse reaction is a cellular immune response that happens mostly in tuberculoid and borderline cases and is clinically characterized by the appearance of erythema and infiltration in pre-existing lesions (Th1-type response). The type 2 reaction or erythema nodosum leprosum (ENL) is a systemic inflammatory reaction reflecting a humoral immune response to the deposition of immune complex, occurring mostly in lepromatous form and in some borderline cases (Th2-type response). Clinical manifestations of type 2 reaction are characterized by the association of dermohypodermal nodules and general signs such as fever and edema of extremities [12].

It has been described that certain factors play a role in the onset or aggravation of leprosy reactions such as stress, infections, hormonal factors (pregnancy, breastfeeding, and puberty) [13]. The data concerning these risk factors would permit the identification of potential risk groups and the implementation of a long-term monitoring to reduce morbidity and mortality related to leprosy.

In Madagascar, the prevalence of leprosy reactions is continuously increasing, yet no studies on these reactions have been done. The objectives of this study were to describe the epidemiological and clinical profiles of leprosy and leprosy reactions and secondly to determine the risk factors associated to leprosy reactions.

2. Methods

This study was conducted over a 10 years period from January 2012 to December 2021 in the Dermatology Department of the University Hospital Joseph Raseta Befelatanana in Antananarivo, Madagascar. It is a reference center for leprosy in terms of diagnosis and treatment, receiving difficult and referred cases of leprosy. Patients were recruited during a dermatology consultation or a hospitalization. We conducted a retrospective case-control study to compare patients with leprosy reactions and those who did not have these reactions. Cases patients were newly detected leprosy diagnosed with type 1 reaction or type 2 or mixed at baseline. Controls were newly detected leprosy patients without these complications at the time of initial diagnosis. We compared one case with two controls. The patients with incomplete medical records and the patients lost to follow-up were excluded from study. Baseline Data from all patients enrolled regarding the demographic details, clinical features, treatment and complications were reviewed and recorded on a survey form. Univariate and multivariate logistic regression were used to analyze risk factors for leprosy reactions. Only variables with a p value < 0.10 in the univariate analysis were included in the multivariate analysis. The adjusted odds ratio (aOR) with its 95% confidence interval (CI) and the p value were the main measures of association for the multivariate analysis, and a significance level of $p < 0.05$ was assumed.

Ethical considerations: There was no conflict of interest regarding ethics during the preparation of this article. This study was conducted after obtaining the written and informed consent signed by the patients and the agreement of the Director of the University Hospital Joseph Raseta Befelatanana.

Limits: The first limitation of this study is related to its non-representative type. Due to the small numbers of patients, it does not reflect the global situation of the whole Madagascar. Consequently, it is difficult to make correlations with confidence. Furthermore, the follow up time in our study was short in order to assess the long-term evolution of leprosy and leprosy reactions. To deal with these problems, a prospective study with a larger population and a long term of follow up could be conducted.

3. Results

3.1. Epidemiological Profile

In total, 178 leprosy patients were followed up in the Dermatology Department of the University Hospital Joseph Raseta Befelatanana where 161 patients were eligible for this study. Out of the 161 patients, 53 patients who had leprosy reactions were included as cases (33%) and 108 patients without these reactions were recruited as controls (67%). Twenty-seven patients were excluded: 17 patients had incomplete or unexploitable medical records, 10 patients were lost to follow-up. The mean age of the patients was 35.8±15.47 years (with extremes of 8 and 75 years). There was 91 (56.50%) men and 70 (43.50%) women, with a sex ratio of 1.3. Majority of the patients was from the capital city Antananarivo (52.80%). Patients working in the primary sector were the most frequent with a rate of 42.12%, followed

by patients with no income generating activities in 21.01%, patients working in the secondary sector represented 16.34% of cases, patients who are still student in 12.17% of cases and patients working in the tertiary sector in 8.36% of cases.

3.2. Comorbidities

The pathologies associated with leprosy were in order of frequency: arterial hypertension in 5.59% of cases, pulmonary tuberculosis in 2.48% of cases, diabetes in 1.86% of cases and HIV in 0.62% of cases.

3.3. Clinical Aspect of Leprosy

The clinical form borderline lepromatous (BL) was the most frequent followed by borderline tuberculoid (BT), lepromatous (LL), borderline borderline (BB), and tuberculoid (TT) with respectively 47 cases (29.20%), 44 cases (27.30%), 42 cases (26.10%), 18 cases (11.20%), 10 cases (6.20%). The prevalence of clinical form according to Ridley Jopling classification is shown in the Table 1. Ninety-two patients (57,15%) received the multibacillary (MB) treatment regimen, while 69 patients (42.85%) received the paucibacillary (PB) form. Patients with more than 5 skin lesions accounted for 84.47% of cases (136 patients). The prevalence of neurological sequelae was 43.47% where 33 patients (20.49%) had a grade 2 sequelae. Out of the 161 patients, 75 patients (46,58%) had a positive bacteriological index (BI). The epidemiological and clinical profile of leprosy is shown in the Table 2. All patients underwent polymerase chain reaction (PCR) testing. It came back positive in 67.08% of cases with detection of wild strains. Only one case of ciprofloxacin resistance due to an A91V mutation in the *gyr A* gene was reported. No cases of resistance to rifampicin or dapsone were identified. A mean duration of 25.7±6.84 months were found for patients treated with multibacillary therapy (MDT).

3.4. Leprosy Reactions

In this study, 53 cases (33%) of leprosy reaction were documented. The majority of leprosy reactions occurred during the first 6 months of treatment (23 cases or 43.8%). The average time to develop leprosy reactions after the initiation of MDT was 5.80±3.91 months. A leprosy reaction was observed at the diagnosis of leprosy in 11 cases (21%). Out of the 53 cases of leprosy reaction, there were 22 cases of type 1 reaction (41.50%), 24 cases of type 2 reaction (45.28%) and 7 cases of mixed reaction (13.20%) (Figure 1). The BL form was the most frequent clinical form in type 1 and type 2 reaction, found respectively in 9 and 15 patients, followed by the BT form in type 1 reaction and the LL form in type 2 reaction. For the mixed type reaction, the two predominant forms were BL and LL (Figure 2). The commonest clinical sign of type 1 reaction was the association of infiltrated erythematous macules and neuritis in 50% of cases (Figure 3). Concerning the type 2 reaction, the association of erythematous papulonodules and neuritis predominated in 41.66%. Isolated ENL were found in 29.17% patients. Other lesions such as ulcerated skin lesions and erythema multiform-like occurred in 8.33% of cases (Figure 4). Regarding the neurological outcome of the patients, partial recovery of nerve damage was noted in 23% of cases. The neurological condition was unchanged in 28.3% of cases, worsened in 22.1% of cases, and unspecified in 18.7% of cases. The Table 3 summarizes the clinical aspect of leprosy reactions.

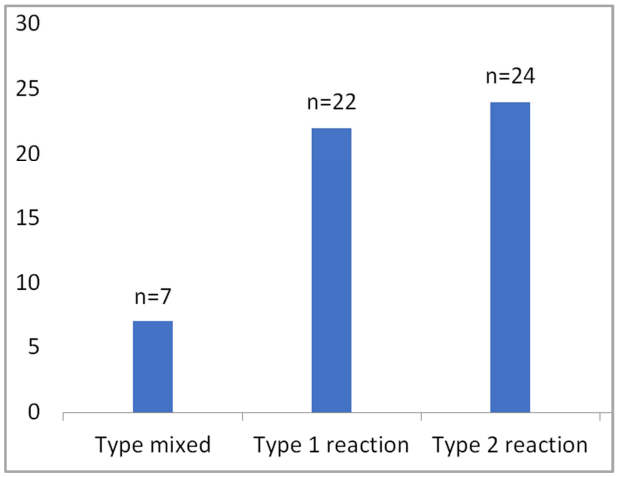


Figure 1. *Distribution of patients according to the type of leprosy reaction.*

Table 1. *Distribution of patients according to the clinical form of Ridley Jopling.*

Clinical form	Case n=53 (%)	Control n=108 (%)
Tuberculoid (TT)	0 (0,00)	10 (9,26)
Borderline Tuberculoid (BT)	8 (15,09)	36 (33,33)
Borderline borderline (BB)	3 (5,66)	15 (13,89)
Borderline lepromatous (BL)	27 (50,9)	20 (18,52)
Lepromatous (LL)	15 (28.30)	27 (25,00)

Table 2. *Epidemiological and clinical characteristic of leprosy.*

	Number of patients (n=161)	Percentage of patients (100%)
Mean age	35,8±15,47 years	
Gender		
Male	91	56,50
Female	70	43,50
Residence		
Antananarivo	86	53,40
Other	75	46,60
Leprosy contact		
Yes	7	4,34

	Number of patients (n=161)	Percentage of patients (100%)
No	154	95,66
Clinical form of leprosy		
TT	10	6,20
BT	44	27,30
BB	18	11,20
BB	47	19,20
LL	42	27,30
Bacillary index		
Positive	75	47
Negative	86	53
Treatment regimen		
PB	64	39,75
MB	97	60,25
Leprosy reaction		
Yes	53	33
No	108	77
Sequelae		
Grade 0	91	56,50
Grade 1	37	22,98
Grade 2	33	20,49

Table 3. *Epidemiological and clinical characteristics of leprosy reactions.*

	Number of patients (n=53)	Percentage of patients (100%)
Mean age	36±13,53 years	
Gender		
Male	40	75,47
Female	13	24,53
Leprosy reactions		
RR	22	41,50
ENL	24	45,28
Mixed	7	13,20
Onset of reactions		
At the first visit	11	21
During treatment		
0-6 months	23	43,8
>6-12 months	8	15
>12 months	5	9,4
After release from treatment	6	11

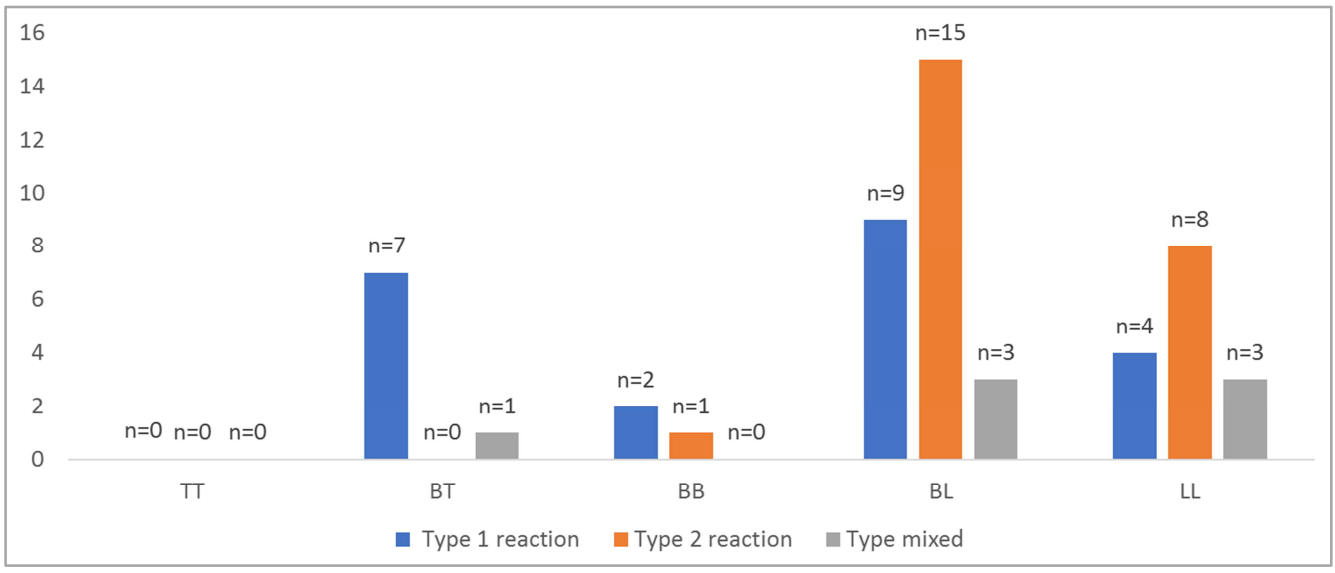
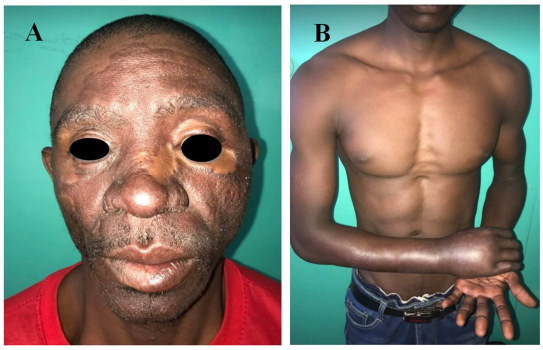


Figure 2. *Distribution of patients presenting leprosy reactions according to the clinical form of Ridley Jopling.*



(A) Infiltrate erythematous on the face, (B) Peripheral neuritis on the upper limb

Figure 3. *Clinical manifestations of type 1 reaction.*

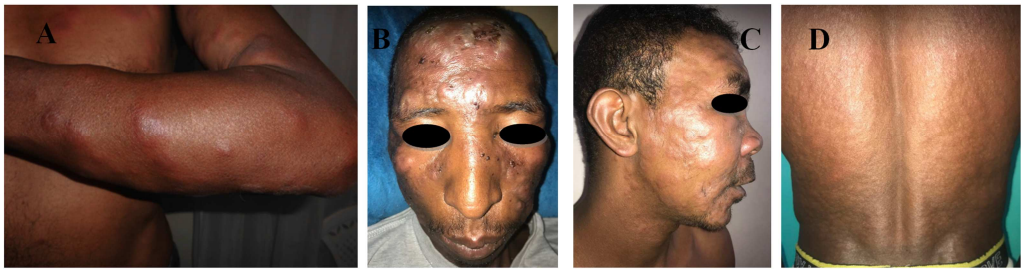


Figure 4. *Clinical manifestations of type 2 reaction.*

(A) Erythema nodosum leprosum on the limbs, (B) Ulcerobullous lesions on the face, (C) Erythema multiforme-like on the face, (D) Urticarial lesions on the trunk

3.5. Risk Factors of Leprosy Reactions

Concerning the univariate analysis, a significant association (p value < 0.10) between clinical variables and the occurrence of leprosy reaction was found such as male gender, presence of high number of skin lesions, positive BI, MB treatment regimen, and poor adherence to treatment. Among them, 4 significant risk factors were associated with leprosy reactions when using multivariate analysis (Table 4): male gender [OR=2.64 (95% CI: 1.80-9.57), p=0.02], positive BI [OR=3.53 (95% CI: 2.41-48.98), p=0.02], MB regimen treatment [OR=8.87 (95% CI: 1.23-3.57), p=0.008)], and poor adherence to treatment [OR=1.97 (95% CI: 1.34-12.95), p=0.0354].

Table 4. *Multivariate analysis.*

Variables	Case n=53 (%)	Control n=108 (%)	aOR (95% CI), *p* value
Male gender	40 (75,47)	51 (47,22)	2,64 (1,80-9,57), p=0,02
MB treatment regimen	45 (84,91)	47 (43,52)	8,87 (1,23-3,57), p=0,008
Positive BI	35 (66,04)	40 (37,04)	3,53 (2,41-48,98), p=0,02
Poor compliance treatment	28 (52,83)	35 (32,41)	1,97 (1,34-12,95), p=0,0354

4. Discussion

The morbidity of leprosy is related to the high number of skin lesions in the MB form [14], the leprosy reactions [15], and the nerve damages [16], which are the main complications of leprosy disease. It is important to identify the clinical features that can predict these deleterious complications. Leprosy reactions are an acute systemic inflammatory complication that occurs in treated and untreated leprosy and can be a functional and life-threatening emergency. Type 1 reaction and type 2 reaction are the two major clinical forms of leprosy reaction. These reactions have different immunological mechanisms, but both are poorly understood, and their initiating factors remain undetermined. The diagnosis and treatment of leprosy reactions remains a challenge for dermatologists [17-19]. As *M. leprae* affects the peripheral nerves, inflammation during leprosy reactions often causes severe nerve damage with a risk of paralysis and permanent functional impairment. To limit these leprosy-related morbidities, early detection of signs of leprosy reactions is essential.

4.1. Epidemiological Profile

The present study found that the age group of 15-45 years is predominantly represented. This finding could be explained by the fact that the incubation period of leprosy is too long, ranging from 2 to 10 years or even 20 years, most cases occur then in young adults, whereas the infection was mainly during childhood [20]. The proportion of children under 15 years of

age in our study was 6.20% (10/161). This is similar to the result of two studies conducted in Brazil which found a prevalence of 8% (39/488) and 7.5% (23/307) respectively [9, 21]. In other words, the low prevalence of leprosy in children is explained by the low rate of detection and reporting of leprosy cases in the pediatric population [22]. However, the number of pediatric leprosy cases is an indicator of persistent transmission in the community [6]. In 2019, among 1 283 new leprosy cases in Madagascar, there were 255 pediatric cases with grade 2 of disability [6]. There was a male predominance in our study, corresponding to 56.50% of leprosy patients, which is consistent with the data from African studies. It was 55,3% in Democratic Republic of Congo, 57,1% in Nigeria and 60,3% in Senegal [22-24]. Several studies have reported this high prevalence of leprosy in males as well as the association of male gender with complications of leprosy such as MB form, leprosy reactions and physical sequelae. Hypotheses including the interaction of genetic and environmental factors would explain this male predominance [21, 25-32].

The study found that patients from the capital city (Antananarivo) predominated in 53.4% of cases which is in line with a report from Thailand [18]. The prevalence of leprosy is high in densely populated areas or urban areas which could be explained by the fact that there, leprosy testing centers are more easily accessible to patients. Geographical constraints that make it difficult to access health centers may reduce the detection rate of leprosy.

4.2. Leprosy Contact History and Comorbidity

Seven patients had a notion of leprosy contact in their past history. A lower rate compared to Emy A Thomas et al, who found 17 cases [28]. The transmission of leprosy is human-to-human and depends on the immunity of each individual. In addition to genetic factors, risk factors for leprosy would include promiscuity and poverty.

The current study found co-infection of leprosy and pulmonary tuberculosis in 2.48% (4/161). In a study conducted by Kumar et al, this association was more frequent in 7.7% of cases (9/117) [33]. Pulmonary tuberculosis and leprosy are two endemic diseases in Madagascar. However, co-infection with the two mycobacteria remains rare. Two to six cases of concomitant infection with *M. leprae* and *M. tuberculosis* per 100,000 inhabitants can be detected per year in Madagascar [34]. Tuberculosis occurs approximately 2 months to 10-15 years after the diagnosis of leprosy, and rarely before the diagnosis of leprosy [35]. Pulmonary tuberculosis often occurs after systemic corticosteroid. In our study, 3 cases of pulmonary tuberculosis complicated the treatment of a leprosy reaction with long-term systemic corticosteroid. One patient was diagnosed with pulmonary tuberculosis at the diagnostic of leprosy. On the other hands, some authors suggested that an antigenic cross-reaction secondary to *non-M. leprae* mycobacterial infection such as tuberculosis could provoke a type 1 reaction. Due to their broader memory T cell repertoire, it is, thus plausible that adults show more frequent type 1 reaction that are triggered by cross reaction to *M. leprae* antigens following sensitization by *non–M. leprae* mycobacterial infection [36].

4.3. Clinical Aspect of Leprosy

According to the WHO classification, MB form was the commonest (57,15%) clinical presentation of leprosy in our study which is in agreement with the data found in literature about leprosy reactions (91.5% for the Democratic Republic of Congo, 77% for Guinea, 86.5% for North India) [22, 26, 37].

4.4. Leprosy Reactions

The prevalence of leprosy reactions in this study was 33% compared to 71.4% and 15.6% as reported respectively by Jacob et al and Cuellar-Barboza et al [38, 39]. This finding demonstrates that the prevalence of leprosy reactions differs widely according to geographical and epidemiological parameters and varies between 6 and 67% for type 1 reaction [36]. It is therefore difficult to compare the frequency of leprosy reactions between different countries. Several factors that could lead to this variation in the prevalence of leprosy reactions have been pointed out and suggested, such as different case definitions (e.g. excluding or including pure neuritis), different method of diagnosis, duration of MDT treatment which vary from one country to another [18, 36].

Leprosy reactions were predominantly in males (75.47%) and in the age group of 30-45 years (%). The average age of patients with leprosy reactions was 36±13.53 years compared to 45 years as reported by Suchonwanit et al [18]. Type 1 and type 2 reaction came with almost equal frequency in 41.50% and 45.28% respectively which is comparable to Jacob et al's data [39]. The prevalence of each type of reaction varied from one country to another. Emy A Thomas et al in India and Suchonwanit et al in Thailand found a predominance of type 1 reaction (32.5/44.8% of cases and 38.9/56.5% of cases) [18, 26]. These results contrast with some authors' results who found a predominance of type 2 reaction such as Cuellar-Barboza et al and Penna et al (80.8% and 58.5% of cases) [25, 38].

In our study, leprosy reactions were seen in patients at the time of diagnosis as well as during treatment. The reactions were commonly found within six months after starting treatment (43,8%). This finding is in accordance with the result of a study conducted by Rodrigues et al [40]. It is well known that reactions were more likely to happen during treatment. This would suggest that treatment itself can trigger reactions [41, 42]. The efficacy of MDT in destroying *M. leprae* is thought to result a massive release of antigen that causes inflammatory reactions [18]. Besides, recent studies show strong evidence that susceptibility to leprosy reactions is also controlled by genetic factors, more specifically the genes encoding tumor necrosis factor, mannose binding lectin, vitamin D receptor are responsible of the appearance of reactions before treatment as well as their clinical polymorphism [42, 43]. In this study 21% of patients developed leprosy reaction at the first visit. The BL form was the most common clinical form in both types of leprosy

reaction followed by the BT form in the type 1 reaction and the LL form in the type 2 reaction. This result is similar to a study in Pakistan done by Tabassum et al [44].

In this study, mixed skin-neurological involvements were frequent in type 1 and type 2 reactions, present in 51.7% and 41.9% of cases, respectively. Data collection from the study conducted by Scollard et al separated the neuritis occurring alone from those occurring during reactions. They conclude that neuritis is a complication of leprosy that is often not associated with inflammatory skin lesions and other symptoms of reaction [9]. This specific type is often called silent neuritis, where symptoms are characterized by a sensory or motor deficit without associated cutaneous signs of type 1 and 2 reaction [45]. Pure neuritis was found in 4.54% of cases in our study. Ranque et al reported that the first sign of nerve damage was pain in 77.1% of cases, and 41% of patients had a sensory and motor deficit [36]. These findings remind that even there is no skin reaction, examination of nerves should always be performed on each patient's visit to detect early signs of nerve inflammation.

Corticosteroids remain the pillar of first-line therapy for type 1 reaction. In countries where thalidomide is not available, it is also the mainstay of type 2 reaction treatment. This is illustrated in our study where all patients with leprosy reactions received oral corticosteroid 40 to 60mg. The mean duration of corticosteroid therapy was 12.5±3.5 months (18.5±18.7 months for the type 2 reaction and 14.7±12.1 months for the type 1 reaction) compared to 10.73±7.66 months (13.89±13.57 months for the type 2 reaction and 9.61± 6.38 months for type 1) as a study conducted by Emy A Thomas et al [26]. In the present study, majority of leprosy reactions required prolonged course corticosteroid-therapy and some patients received doxycycline in addition. The duration of treatment was longer than recommended which may be caused by the corticosteroid-dependence of leprosy reactions. Other factors contributing to this duration of treatment could be the prolonged response to corticosteroid as symptoms of leprosy reactions may last over months, and the lack of criteria for determining the beginning and the end of reactions [46]. Our study reported a better improvement of skin symptoms (74%) than nerve impairment (31%), after steroid therapy for leprosy reactions. A high prevalence of neurological sequelae was found at 43.50% of cases where a grade 2 sequelae was seen in 20.50%. Unlikely, a lower prevalence was reported by Oliveira et al (29.8%) [21]. This high frequency of neurological sequelae in our study could be explained on the one hand by the delay in referral and management of leprosy due to diagnostic erraticism and on the other hand explained by the fact that our center received referred difficult cases often seen in the advanced stage.

Our study identified 4 significant risk factors associated with leprosy reactions. These were male gender, poor adherence to treatment, multibacillary clinical form, and positive BI status which was similar results with studies published in the literature [9, 33, 39, 45, 47, 48]. Poor compliance with treatment was an independent risk factor for leprosy reaction. This is the major original finding of our study that has not yet been reported in the literature.

A study conducted by Antunes et al in 2013 on 440 leprosy patients assessed clinical and biological risk factors for leprosy reactions. At the time of diagnosis, the risk factors identified were positive BI or PCR in skin smears, anti-phenolic glycolipid-1 ELISA, hyperleukocytosis, thrombocytopenia and elevated lactate dehydrogenase. After treatment, positive BI or PCR in skin smears, anti-phenolic glycolipid-1 ELISA, anemia, hyperleukocytosis, thrombocytopenia were the risk factors for leprosy reactions [46]. Ambrosano et al reported that in multibacillary cases, like Virchowian patients, the slow elimination of dead bacilli and thus the continuous presence of their antigens increased the risk of leprosy reactions [19].

5. Conclusion

This study showed the epidemiological and clinical profile of leprosy reactions in patients treated at the University Hospital Joseph Raseta Befelatanana over a period of 10 years. The significant prevalence and frequency of severe complications, such as reactions and neurological sequalae emphasize the importance of the determination of risk group and the need for long term monitoring of these patients. It was found that 4 major risk factors were significantly associated with leprosy reactions: male gender, poor treatment compliance, positive BI, and MB treatment regimen. Since failure to treat reactions can leave sequelae, early detection and treatment of all cases, before disabilities occur, remains the fundamental strategy. Attention is drawn to the fact that dermatologist play a major role in the care given to the patient even if diagnosis and management of leprosy reactions are still challenging. A prospective study with a larger population and a long term of follow up could be conducted in the future to improve research on leprosy reactions.

Conflict of Interests

The authors declare that they have no competing interests.

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