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Original Article

Relapse in Leprosy in Post-elimination Phase: Scenario from a Tertiary Care Center in South India

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The primary aim of this study was to study the relapse rate in the post-elimination phase of leprosy and the secondary aim to study the clinical features of the relapsed cases in a Tertiary Care Centre in Thiruvanthapuram, South India. This was a 10 year retrospective study of relapsed cases of leprosy in the post-elimination phase. There were 39 cases of relapse in the 10 year (2006-2015) study period, with a relapse rate of 10.03%. Out of 39 relapses, 8 were PB cases and31 were MB cases. There were 33 males (84.61%) and 6 females (15.39%) with a male/female ratio of 5.5:1. The mean age was 46.82 years and age group 41-50 constituted the maximum number of cases 11 (28.21%). Borderline tuberculoid (BT) was the commonest initial type of leprosy to relapse, 17 cases (43.58%), while the commonest type in the relapsed state was also BT, 18 cases (46.15%). BT relapsing as BT was the commonest type, 13 cases (33.33%). Relapse was more common in smear positive cases, 21 (53.85%), compared to smear negative cases, 18 (46.15%). Twelve (12/21, 57.14%) relapses in smear positive cases (BI 4+) were in those who were treated with FDT for one year. This study shows a high prevalence of relapse cases in the post-elimination phase in cases treated in a tertiary care settings which indicates the need of in-depth studies to find out determinants such as subsets of cases at higher risk of getting relapse and duration of treatment in such cases as well as long term steroids.

Key words: Relapse, Post-elimination, Borderline tuberculoid

Introduction

The Government of India on December 31, 2005 declared leprosy to be "eliminated" as a public health problem by attaining the WHO parameter of prevalence less than 1 in 10,000. However it is a fact that new leprosy cases are still being encountered, including smear positive cases. Relapse in leprosy is defined as the appearance of new signs and symptoms of leprosy in a patient who has been adequately treated with the full course of WHO recommended multidrug therapy (MDT) and deemed "cured" (Kaimal and Thappa 2009). However even in the post-elimination phase of leprosy relapse cases of leprosy are being encountered. Moreover in the post-elimination phase there are no procedures to document relapse due to integration of anti-leprosy services into the general health

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programmes. Relapsed cases of leprosy may be important sources of infection to their immediate contacts (Moet et al 2004). Relapse may be indicator of the inadequacy of regimen to some patients and also quality of anti-leprosy services resulting in irregular/inadequate treatment. There is a paucity of studies regarding relapse of leprosy in Kerala in the post-elimination phase of leprosy. We do see cases of relapse in the urban leprosy center of our tertiary care institute and hence we undertook this study. The primary objective of this study was to estimate the relapse rate and the secondary objective to study the clinical and epidemiological features of the relapsed cases.

Materials and Methods

This was a 10 year retrospective (2006-2015) study of all new relapsed cases of leprosy in the Urban Leprosy Center (ULC) of our Tertiary Care Institute. Data collection: Data were collected from the pre-formatted cards of our urban leprosy center provided by the National leprosy eradication programme (NLEP).

Study population

This study included all the new relapsed leprosy cases in the study period. A case of relapse was defined as the appearance of definitive new skin lesions, extension of previous skin lesions, new nerve thickening, previous smear negative becoming positive, an increase of Bacterial index (BI) by 2+ from the previous value, histopathological evidence like new granulomas in PB cases and infiltration of macrophages with positive acid fast bacilli (AFB) in MB cases, in patients who had successfully completed WHO recommended MDT which was 6/9 pulses in pauci-bacillary cases (PB) and 12/18 pulses in multi-bacillary cases (MB) (Kaimal and Thappa 2009).

The clinical and the epidemiological features of the relapsed cases were studied in detail. The main demographic details studied were age, sex, and duration of relapse from the time of release from treatment (RFT). Special features like regularity/irregularity of treatment, defaulters and use of systemic steroids for lepra reactions were studied in detail. The leprosy cases were classified by combining the Ridley-Jopling (Ridley and Jopling 1966) and Indian Association of Leprologists systems (IAL 1982). Smear positive cases were expressed in terms of Bacteriological index (BI) and morphological index (MI). Histopathology slides of the cases were reviewed to see if the clinical diagnosis matched with the histopathology.

Data analysis

The data collected were analyzed in terms of mean, frequency and percentage. The relapse rate was calculated by dividing the total number of relapse cases in the study period by the total number of new leprosy cases in the study period and multiplied by 100. The Chi-squared test was used for assessing statistical significance and a '*P*' value of less than 0.05 was considered significant.

Permission to conduct this study was sought from the Institutional Review Board of this institute who stated that since this was a retrospective, case records based study with no direct patient involvement, permission was not required.

Results

In this 10 year retrospective study in the post-elimination phase of leprosy (2006-15), there were a total of 389 new leprosy cases (n=389). Out of this there were 285 multibacillary cases and 104 paucibacillary cases according to the WHO classification. 45 cases of multibacillary case which presented as BL or LL were given 2 years MB-MDT. There were 39 cases of relapse in the 10 year study period, thus accounting for a relapse rate of 10.03% (39/389). Out of this 8 were PB cases and 31 were MB cases. In the

relapse cases, there were 33 males (84.61%) and 6 females (15.39%) with a male/female ratio of 5.5:1. The mean age was 46.82 years, the oldest 63 years of age and the youngest 25 years. The age group 41-50 constituted the maximum number of cases 11, (28.21%). The mean duration of relapse from date of RFT was 3.10 years, the longest being 8 years and the shortest 4 months. In the relapsed cases 3 (7.69%) were irregular in treatment, there was 1 defaulter (2.56%) and 5 cases (12.82%) were on systemic steroids for lepra reactions.

Table 1 : The initial types of leprosy and type in relapsed state (n=39)

Initial type of leprosy	Frequency	Percentage	Type in relapsed state	Frequency	Percentage
Borderline tuberculoid	17	43.59	Indeterminate	3	7.70
Borderline borderline	1	2.56	Pure neuritic	3	7.70
Borderline lepromatous	7	17.95	BT	18	46.15
Lepromatous leprosy	14	35.90	BB	1	2.56
			BL	4	10.26
			LL	8	20.52
			Histoid	2	5.13

Table 2 : Showing the number and frequency of initial type of leprosy and relapsed type of leprosy and treatment given (n=39)

Initial type of leprosy	Relapsed type of leprosy	Number	Percentage	Treatment given
BT	BT	13	33.33%	10-MB, 3-PB
LL	LL	6	15.38%	MB
LL	BL	3	7.69%	MB
BL	BT	3	7.69%	MB
LL	Histoid	2	5.12%	MB
BL	LL	2	5.12%	MB
BT	BL	1	2.56%	MB
LL	I	1	2.56%	PB
LL	PN	1	2.56%	MB
LL	BT	1	2.56%	MB
BL	I	1	2.56%	PB
BL	PN	1	2.56%	MB
BL	BB	1	2.56%	MB
BB	BT	1	2.56%	PB
BT	I	1	2.56%	PB
BT	PN	1	2.56%	PB

The initial types of leprosy which relapsed and the type of leprosy in the relapsed states are given in Table 1. The frequency and percentage of the initial types of leprosy and the type of relapsed leprosy are given in Table 2. Borderline tuberculoid (BT) was the commonest initial type of leprosy to relapse, 17 cases (43.58%), while the commonest type in the relapsed state was also BT, 18 cases (46.15%). BT relapsing as BT was the commonest type of relapse, 13 cases (33.33%), followed by lepromatous leprosy (LL) relapsing as LL, 6 cases (15.38%). There were 3 cases (7.69%) of pure neuritic leprosy (PN) and 3 cases (7.69%) of indeterminate leprosy in the relapsed cases. Relapse was more common in leprosy cases who were initially smear positive, 21 (53.85%), compared to smear negative cases, 18 (46.15%). However in the spectrum of the relapsed cases, smear negative cases were more common, 25 (64.10%) than smear positive cases, 14 (35.90%). 12/21 (57.14%) relapses cases were treated with Fixed Duration Treatment (FDT) for one year.

Lepra reactions were seen in 9 cases (23.07%) which included 3 Type 1 reactions and 6 Type 2 reactions. Grade 2 disability were seen in 14 cases (35.89%), out of which 4 cases (10.26%) were new cases of disability while the rest were sequele of old disease. In the relapsed cases, 8 (20.51%), were given PB treatment and 31 (79.49%) were given MB treatment.

Discussion

This 10 year retrospective study detected a relapse rate of 10.03% in the post-elimination phase of leprosy in cases being treated at a Tertiary Care centre. This is significantly higher than WHO estimates (WHO 1995). The WHO estimates for relapse in leprosy following MDT is 0.77% for MB cases and 1.07% for PB cases (WHO 1995). Studies regarding relapse rates ranges from 0 to 20% (Jamet and Ji 1995, Gebre et al 2000). However, proper comparison is not possible as there is no uniformity in the parameters in various studies, as some have used relapse rates, while others have used relapse per person-years. However by any standard the relapse rate in this study was very high. This study was done in a tertiary care referral center and it is possible that in the post-elimination phase of leprosy due to the integration of anti-leprosy services with the general health service, more cases of advanced disease come to or referred to our tertiary care center. This could explain the high prevalence. Still then a high relapse rate in an area declared to be “eliminated” from leprosy is should be cause of concern for the national control programme. A study in Columbia showed a relapse rate of 20% in MB case (Guerrero et al 2012). A similar study done in Philippines showed a relapse rate of 0.3% in MB cases (Maghanoy et al 2011), while a study done in China showed a relapse rate of 0.21% in MB cases (Shen et al 2006). However in the latter study the cases were given 24 months FDT. It is a well known fact that the relapse rate with 24 month FDT is very low in MB cases. In the present study the relapse rate was more common in MB cases (7.97%) then the PB cases (2.06%). While some studies have shown relapse more in PB cases (Prabu et al 2015), others in North India have also reported a high relapse rate in MB cases treated with one year FDT (Kumar et al 2013). This can again be attributed to the fact, that in the post-elimination phase of leprosy since most of anti-leprosy services were integrated into the general health services, MB being more florid in nature, were referred to tertiary care centers like our institute. The present criteria for classifying into PB and MB, allows for even smear negative cases to be included under MB, if there are 6 or more lesions. In the present

study males outnumber females by a ratio of 5.5:1. This is similar to most other studies. In any geographic area the prevalence of leprosy is more in males and hence we expect the relapse rates to be more in males (Shen et al 2006, Prabhu et al 2015, Ali et al 2005). The mean age was 46.82 years and this is similar to most other studies (Ramu 1995). Relapse was much more common in patients >45 years of age and this was statistically significant ('*P*'=0.003). However in the study done in Philippines the mean age was less, 30 year, (Maghanoy et al 2011). This is because the in Philippines there is a robust and efficient state sponsored programme to detect leprosy in all age groups.

The mean duration of relapse from time of RFT was 3.10 years. This is similar to other studies (Shen et al 2006, Prabhu et al 2015). This fact indicates that in patients who do not relapse within 3 years, then the chance of relapse after 3 years is unlikely. The practical significance of this fact is that leprosy cases after RFT may require follow up for at least 3 years. Unfortunately in the post-elimination phase there is no scope for follow up. In the present study a patient relapsed after 8 years. A long duration of relapse after RFT may be difficult to distinguish from re-infection, as infection with *M.leprae* does not give protective immunity against subsequent infection. However molecular techniques to distinguish between relapse and re-infection have been studied, which unfortunately is available only in few centers (Desikan 1995). BT was the commonest type of leprosy to relapse in this study (43.58%), but this was not statistically significant ('*P*'=0.907). This is because the commonest type of leprosy encountered in our center is the BT type. This is in accordance with other studies (Kaimal and Thappa 2009). In relapsing types of leprosy again BT was the commonest type (46.15%), but not statistically significant ('*P*'=0.141). BT relapsing as BT (33.33%) was the commonest pattern seen in the present study (Table 2).

The prevalence of leprosy relapsing as pure neuritic (7.69%) and Indeterminate leprosy (7.69%) was low in this study. However, leprosy cases relapsing as PN can present with clinical difficulties as we have to ensure that these nerves were not previously affected, if not properly documented. Presence of granulomas or macrophages in the nerve biopsy may help in the diagnosis (Job 1995). Interestingly all the relapsed cases as PN in this study were previously not PN type (Table 1.)

In the present study relapse was more common in leprosy cases which were initially smear positive, (53.85%) and this was statistically significant ('*P*'=0.005). All of these cases had an initial BI of 4+ and more. This is similar to other studies also. However in the relapsed spectrum majority of the cases were smear negative (64.10%). This supports the fact that following anti-leprosy therapy the immunity of the body improves and hence accounts for the increased prevalence of tuberculoid type in relapsed cases who were previously smear positive. In this study it was also found that relapse was more common in smear positive cases treated with 1 year FDT, than 2 year FDT (57.14%). This has been observed in other studies also (Jesudasan et al 1996, Girdhar et al 2000). Increased prevalence of smear positive cases in relapsed leprosy in the post-elimination phase forms a major stumbling block for the NLEP as they are the “open” infective cases who can transmit leprosy. Moreover this study and other studies have shown that the 1 year FDT for smear positive cases, especially if the initial BI is more than 4+ is not sufficient and they are likely to relapse (Baohong 2001, Shetty et al 2011). Such cases should be treated beyond 1 year and the previous regime of 2 year FDT has shown very low

levels of relapse. WHO in the 8th operational guidelines has also suggested that if the initial BI is 4+ or more MDT can be continued beyond 1 year if regular clinical and bacteriological follow up is possible (WHO 2012).

The prevalence of new grade 2 disability in relapsed cases was 10.26%. This is also unfortunate as we are in the "elimination phase" and the stigma associated with leprosy is due to the disability/deformity. Relapse in leprosy occurs more common in defaulters, irregular treatment and inadequate treatment. However in the present study irregular treatment and defaulters did not significantly contribute as they accounted for only 7.65% and 2.56% respectively. Persisters and drug resistance are other causes for relapse (Sehgal et al 1996). There are no facilities to diagnose drug resistance in this institute. In this study, cases which relapsed as PB were given PB treatment and cases which relapsed as MB were given MB treatment, without changing the regime. All of these patients responded, indicating indirectly that drug resistance was not the cause for relapse. However 12.82% of the relapsed cases were previously on systemic steroids for lepra reactions and steroids are well known to cause replication of persisters. Hence a good percentage of relapse in the present study could be due to persisters.

Limitations of the study

Clinical findings and statistical data from a tertiary care center may not always represent the general trend in population as these centers are referral centers and even some of the self reporting cases may be reporting late. It is also possible that a large number of relapse cases were referred to this tertiary care center as new cases without being treated in minor hospitals due to lack of specialists, since anti-leprosy services are now integrated in the general health programmes in the post-elimination phase of leprosy.

Conclusions

This study detected a high relapse rate of leprosy in the post-elimination phase of leprosy, the commonest type of leprosy to relapse was BT, further the commonest type of leprosy in the relapsed state was BT, BT relapsing as BT was the commonest pattern, relapse was more common is smear positive cases, relapses were common in smear positive (having initial BI 4+) cases given 1 year FDT. The number of defaulters and irregular treatment cases were not significant in this study.

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