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Original Article

Do Systemic Steroids Given for Lepra Reactions Increase the Risk of Relapse after Release from Treatment?: A 10 year Retrospective Study from a Tertiary Care Centre

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Relapse in leprosy is attributed to the multiplication of the persisters, inadequate treatment, default in treatment and due to drug resistance. The primary objective of this study was to determine if intake of systemic steroids for lepra reactions during the treatment phase of leprosy contributes to relapse later after release from treatment. This is a 10 year retrospective study done in a tertiary care centre of Kerala, South India. There were a total of 499 leprosy cases in this 10 year study. There were 29 cases of relapse with a relapse rate of 5.81%. There were 24 males (82.76%) and 5 females (17.24%) with a male/female ratio of 4.8:1. The commonest spectrum prior to relapse was borderline tuberculoid, 13 cases. In the total number of relapsed cases (29), 13 cases were on systemic steroids prior to relapse and this was statistically significant ('P'< 0.001). However, the duration of steroid therapy in contributing to relapse in respect to less than and greater than 5 months was not statistically significant ('P'=0.118). This study has demonstrated that steroids given for lepra reactions might increase the risk of future relapse in these patients after RFT. However this is a preliminary observation and sample size is small. Hence future studies with larger sample size may through more light on this aspect of leprosy. These patients should be carefully and regularly followed up to detect relapse.

Keywords : Relapse, Reactions, Steroid therapy, Leprosy, Kerala, South India

Introduction

Relapse in leprosy is defined as the re-occurrence of the disease at any time after the completion of a full course of treatment (WHO 2006). The relapse rates in leprosy varies from 0-20% in various studies (Gebre et al 2000, Linder et al 2008). Relapse in leprosy is attributed to the multiplication of the persisters, inadequate treatment, default in treatment and due to drug resistance (Ali et al 2005). Relapse may also occur due to misdiagnosis of multi-bacillary cases as pauci-bacillary cases and giving these cases pauci-bacillary treatment. Relapse also has to be distinguished between late reversal lepra reactions and re-activation of disease. A preliminary observation in this tertiary care centre demonstrated that many relapsed leprosy patients were on systemic steroids for the treatment of lepra reactions previously. Hence we decided to conduct this study. The primary objective of this study was to determine if intake of systemic steroids for lepra reactions during the treatment phase of leprosy contributes to relapse later after release from treatment.

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Materials and Methods

This is a 10 year (2012-2021) retrospective descriptive study done in the urban leprosy centre of Department of Dermatology and Venereology of Government Medical College, Thiruvanthapuram, Kerala, India. Data were collected from the pre-formatted cards of our urbanleprosy centre provided by the National leprosy eradication programme (NLEP) after ethical considerations. This study included all the new relapsed leprosy cases in the study period. The time period to denote relapse was taken as within 3 years after RFT and 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) (Gebre et al 2000, Linders et al 2008, Kaimal &Thappa 2009).

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 last previous value, histopathological evidence like new granulomas in PB cases and infiltration of macrophages with positive acid fast bacilli (AFB) in MB cases. Patients who were defaulters were excluded from the study. By reviewing the NLEP cards if there was indication of wrong classification of multi-bacillary cases as pauci-bacillary cases and hence subsequent relapse, these cases were also excluded from the study. If at time of relapse, there was an active case of leprosy (smear positive case) in the family or contact history of the patient, these cases were also excluded as reinfection was a possibility here. The relapse rate was calculated by dividing the total number of relapse cases by the total number of leprosy cases in the study period and multiplied by 100. Other basic demographic data were also collected. Data were also collected regarding intake of steroid therapy for lepra reactions during the initial treatment phase. The starting dose, the duration of steroid therapy and the indications for steroid were also noted. The data collected were entered in Excel spreadsheet and analysed.

Quantitative variables were expressed as mean and standard deviation. Qualitative variables were expressed as frequency and percentage. Independent sample t-test was used to compare the mean values between 2 different groups and Chi-square test was used for comparing proportion. A 'P' value of ≤ 0.05 was considered statistically significant.

Results

There were a total of 499 leprosy cases in this 10 year study (2012-2021). There were 29 cases of relapse as per the aforementioned criteria in the study period (n=29) with a relapse rate of 5.81%. The relapse rate in BT-PB was 2.61%, while it was 3.20% in BB/ BL/ LL. There were 24 males (82.76%) and 5 females (17.24%) with a male/ female ratio of 4.8:1. There were no childhood cases of relapse. The mean age was 45.10 years. The youngest age was 20 years and the oldest age 68 years. The commonest age group was 41-50 years (8 cases, 27.59%). Prior to relapse, 10 patients (34.48%) had Type 1 lepra reaction and 3 patients (10.34%) had Type 2 lepra reaction (recurrent ENL) All the cases of Type 1 and 2 lepra reactions occurred when the patient was on MDT and there were no cases of late reversal reaction. The remaining 16 patients (16/29) did not have any lepra reactions during their treatment phase prior to relapse. The commonest spectrum prior to relapse was Borderline tuberculoid (13 cases, 44.83%). The type of leprosy and the frequency prior to relapse and type of leprosy after relapse is given in Table 1. BT (13 cases) was the commonest type of initial leprosy and the commonest type of leprosy after relapse was also BT (14 cases). There were no cases of pure neuritic leprosy. In the 3 cases of BL who relapsed the initial BI was 3+ in all the cases and after completing MDT it

Table 1 : Initial type of leprosy and type after relapse (n=29).

Initial type of leprosy	Number	Percentage	Type of leprosy after relapse	Number	Percentage
BT	13	44.83%	BT	14	48.28%
BB	3	10.34%	BL	12	41.38%
BL	3	10.34%	BB	Nil	
LL	9	31.03%	LL	2	6.90%
Histoid	1	3.45%	Histoid	1	3.45%
Total	29			29	

Table 2 : Salient features of leprosy cases and steroid therapy details prior to relapse (n=13).

No.	Age (Years)	Type of leprosy before relapse	Indication for steroid therapy prior to relapse	Starting dose of prednisolone	Total duration in months
1	29	BT	Ulnar palsy	40 mg	5.3
2	50	LL	Recurrent ENL	40 mg	4.5
3	55	LL	Bilateral foot drop	60 mg	7.2
4	43	BT	Claw hand	40 mg	3.5
5	50	BT	Foot drop	40 mg	3
6	52	BT	Ulnar palsy	60 mg	6
7	44	LL	ENL	40 mg	3
8	45	BB	Ulnar palsy	60 mg	5.5
9	38	BT	Claw hand	40 mg	3.6
10	51	LL	ENL	40 mg	4.4
11	48	BL	Facial palsy	60 mg	7.2
12	68	BB	Severe Type 1 reaction	40 mg	3
13	33	BT	Ulnar palsy	60 mg	5.6

was negative in all the cases. There were 9 cases of LL which relapsed. The initial BI in all the cases were 6+, while after completing MDT it was 1+ in 2 cases and no AFB seen in 7 cases.

Thirteen cases (13/29, 44.83%) belonging to the relapsed group were on systemic steroids for lepra reactions prior to RFT and this was statistically significant ('P'< 0.001). The salient features and details of steroid therapy in cases prior to relapse (n=13) are given in Table 2. The mean age of cases who were on systemic steroids was 42.62 years. BT was the commonest type of leprosy who were given steroids prior to relapse (6/13, 46.15%). Nerve palsies was the commonest indication of steroid therapy (9/13, 69.23%). The mean dose of prednisolone given was 43.08 mg. The mean duration of steroid therapy was 4.75 months. However, the duration

of steroid therapy in contributing to relapse in respect to less than and greater than 5 months was not statistically significant ('P'=0.118). Since the mean duration of steroid therapy ws 4.75 months, it is the statistician who advised to make the cut off value < or > than 5 months. A value below 5 months cannot be taken as mean is 4.75.

Discussion

This 10 year retrospective study determined whether systemic steroids given for lepra reactions during the initial treatment period contributed to relapse after release from treatment after other causes of relapse were ruled out. This 10 year retrospective study in a tertiary care centre showed a relapse rate of 5.81%, much lower than a previous study done in the same centre which showed a rate of 10.03% (Nair & Mathew 2017). The dwindling number of cases in the post elimination phase of leprosy could be the cause of this. However the bone of contention is that encountering relapse cases of leprosy in the post elimination phase of leprosy though small in number is a major stumbling block for further control and preventive strategies (Rao et al 2022). BT was the commonest initial type of leprosy to relapse and the commonest type after relpase was also BT. This is in conformance with previous studies (Nair & Mathew 2017). However, 2 cases of relapsed LL were initially also LL. We could not rule out drug resistance in this due to lack of facilities.The causes of relapse in leprosy after standard and adequate therapy are varied and multiple. Defaulters and wrong classification of multibacillary into paucibacillary cases are other situations where we encounter relapse (WHO 2012). Fixed duration therapy (FDT) also contributes to relapse in some cases if the initial bacteriological index (BI) is 4+ or more as 12 month MB-MDT may not be sufficient (Girdhar et al 2000, Liangbin et al 2016). Drug resistance is another important cause of relapse. However, a word of caution should be added regarding re-infection. Re-infection is always possible in leprosy, unlike other diseases leprosy does not give immunity against further infections and this should not be counted as relapse (Stefani et al 2017). It is almost impossible to distinguish between relapse and re-infection within 1 to 3 years after release from treatment since the clinical presentations in both are similar. However, after 3 years re-infection is most likely the cause rather than relapse according to many leprosy workers. In the present study we have eliminated cases of relapse which had a positive family history of open leprosy cases. However, contact from non-family sources could not be ruled out. Late reversal reactions may be confused with relapse, but there are many criteria to distinguish both. An empirical course of systemic steroids may cause the late reversal reaction to disappear, but not a relapse. Re-activation of disease due to inadequate therapy may also be confused with relapse. There are some scoring systems to distinguish between relapse, reactions and re-activation, but these scoring systems have not been validated in prospective studies (Linder et al 2008).

In the present study we have carefully selected the cases of relapse without confounding factors. We have applied the WHO parameters to diagnose relapse. We have eliminated defaulters, inadequate treatment, wrong classification of disease (multibacillary to pauci-bacillary) and reinfection from open cases of family contacts. In this study 13 out of the 29 relapsed cases were on systemic steroids for lepra reactions prior to relapse. We have also taken into account cases who were on systemic steroids for lepra reactions in the study period, but did not relapse and then applied the t-test which was statistically significant ('P'<0.001) . Hence the only remaining risk factor for relapse in this study was systemic steroids given for lepra reactions, thus contributing to relapse as one of risk factors. Therefore we infer

that systemic steroids given for lepra reactions might contribute to relapse after RFT and needs to be kept in mind when monitoring such cases.

Many leprosy workers are of the opinion that the persisters of *M. leprae* is the most important factor contributing to relapse. Persisters are drug sensitive *M. leprae* residing in certain sites of the body like the Schwann cells, iris, striated muscles, lymph nodes, liver and bone marrow, where the penetration of anti-leprosy drugs is deficient and the persisters are usually in a "dormant" stage. Under certain situations, the exact mechanisms not known, the multiplication of these persisters contribute to relapse (Goncalves et al 2019). Moreover immunosuppressive therapy like systemic steroids enhances the multiplication of these persisters. This is also the reason that WHO has advocated to give 50 mg of clofazimine monotherapy in cases of late reversal reactions when systemic steroids are being given after completion of MDT, so persisters may not multiply and clofazimine is at least likely to be active against lepra bacilli when given as monotherapy, would be useful to prevent multiplication of the persisters and also keeping the fact that the least chance of *M. leprae* to develop resistance is to clofazimine. These aforementioned facts were the fundamental basis of this study. This is the most important finding in this study. Surprisingly the role of systemic steroids given for lepra reactions has never been studied regarding its role in contributing to relapse after RFT. Systemic steroids are the drug of choice for lepra reactions which cause motor palsies, recurrent and necrotic ENL and severe Type 1 reactions (Wagenaar et al 2017). Their role in reversing most of the damage in the nerves like reducing granuloma formation is established beyond doubt (Scollard et al 2015). However, taking into account the present study, their ability to cause relapse must be borne in mind as it is possible that they enhance the multiplication of the persisters due to their immunosuppressive effect. Where ever possible alternate therapy should be considered, like thalidomide for recurrent ENL. The newer drugs for lepra reactions like minocycline and apremilast should be studied for their role as alternate therapy for reactions, since they are not immunosuppressive. However, in the present study there was no relation between duration of steroid therapy and relapse (*'P'*=0.118). This may indicate that duration of therapy of immunosuppressive agents may not be the only factor for causing immunosuppression, there are other factors involved, as seen in chemotherapy for cancer patients. The present advocated regime of systemic steroids for reactions, the "flexible protocol", may be superior to the WHO advocated regime, but a higher dose is given and for a longer duration. There is a possibility that the patients given this regime may go for relapse later, even though the present study did not show any relation between duration and dose of steroid therapy. Comparison of the present study with other studies could not be done, as we could not find any other similar study focusing on the role of systemic steroids given for reactions in causing relapse. Any such study should rule out the impact of initial wrong classification, inadequate treatment, treatment default, drug resistance and presence of persisters. To the best of our knowledge this could be the first study of its kind, which has focussed on the role of systemic steroids in causing relapse after release from treatment.

Limitations of the study

This is a retrospective study and the sample size is small. It is also possible that some cases of relapse could be due to re-infection from outside non-family contacts.

Conclusion

This study has demonstrated that steroids given for lepra reactions may increase the risk of future relapse in these patients after RFT. Hence these patients should be carefully and regularly followed

up with clinical examination, bacteriological index, and biopsy to detect relapse. This is a small study and therefore we advocate more future studies with a larger sample size to investigate the role of steroids in causing relapse in leprosy, so that this fact becomes more concrete. There are a number of possible factors leading to relapse such as age, gender, bacterial load, dose and duration of steroids (may be) and the risk cannot be calculated simply by chi squared test. Logistic regression with adequate sample size may be more definitive for calculating the risk. Future studies should analyse these factors.

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