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Leprosy and tuberculosis concomitant infection: A poorly understood, age-old relationship

TIMOTHY MILES RAWSON*, VASEEM ANJUM**, JASMIN HODGSON*, A KAMESWARA RAO**, KRISHNA MURTHY**, PSS SUNDAR RAO**, JONNALAGADA SUBBANNA** & PV RANGANADHA RAO**

**Imperial College, London, UK*

***Lepra India: Health in Action, Hyderabad, Andhra Pradesh, India*

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Summary Historically, archaeological evidence, post-mortem findings and retrospective analysis of leprosy institutions' data demonstrates a high observed incidence of concomitant infection with leprosy and tuberculosis (TB). However, reports of concomitant infection in the modern literature remain scarce, with estimates of annual new case detection rates of concomitant infection at approximately 0·02 cases per 100,000 population. Whilst the mechanism for this apparent decline in concomitant infections remains unclear, further research on this topic has remained relatively neglected. Modelling of the interaction of the two organisms has suggested that the apparent decline in observations of concomitant infection may be due to the protective effects of cross immunity, whilst more recently others have questioned whether it is a more harmful relationship, predisposing towards increased host mortality. We review recent evidence, comparing it to previously held understanding on the epidemiological relationship and our own experience of concomitant infection. From this discussion, we highlight several under-investigated areas, which may lead to improvements in the future delivery of leprosy management and services, as well as enhance understanding in other fields of infection management. These include, a) highlighting the need for greater understanding of host immunogenetics involved in concomitant infection, b) whether prolonged courses of high dose steroids pre-dispose to TB infection? and, c) whether there is a risk of rifampicin resistance developing in leprosy patients treated in the face of undiagnosed TB and other infections? Longitudinal work is still required to characterise these temporal relationships further and add to the current paucity of literature on this subject matter.

Correspondence to: Timothy Rawson, Imperial College, London, UK (Tel: (Mobile) 07891750151; e-mail: tmr07@ic.ac.uk)

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Introduction

Tuberculosis (TB) and leprosy are two ancient pathogens, which have been identified as infecting humans 9000[1] and 4000[2] years ago, respectively. It has been shown from archaeological evidence, post-mortem findings and retrospective analysis of leprosy institutions' data that there is a highly observed incidence of concomitant infection with leprosy and TB.[3–6] However, reports of concomitant infection in modern literature remain scarce.[7–18] Estimation of the annual new case detection rate (ANCDR) in India, where both TB (ANCDR 181 per 100,000 in 2011[19]) and leprosy (ANCDR 10·35 per 100·000 in 2011[20]) remain endemic, suggest that you would only detect 0·019 cases of concomitant infection per 100,000 population. Whilst some have questioned whether this apparent decline in observation is a harmful consequence of concomitant infection,[21] others have suggested that it is the protective effects of cross immunity from infection with one of these organisms.[22] Many experts in the field also feel that there may be no interaction between these closely related organisms and that these observations are simply coincidental, coexistence.

The interaction between TB and leprosy has been relatively neglected in the literature in the modern era. With the development of new evidence surrounding the epidemiological interaction between organisms[21] we aimed to identify current cases of concomitant infection described in the literature and review current evidence in support of each epidemiological theory. We also reviewed our own experience of concomitant infection and based on these experiences raise several questions which future investigation may provide benefit to the delivery of leprosy management, reduce the risk of concomitant infection and also add to other areas of infectious disease management. The latter of which, will become increasingly significant as augmentation of services with other specialist fields continues to increase.

WHAT CASES OF CONCOMITANT INFECTION ARE REPORTED IN THE LITERATURE?

In 1982, Kumar *et al.* observed that TB appeared to occur across the entire spectrum of leprosy.[7] This is supported by case reports in the literature describing cases of TB in: tuberculoid,[11–13] borderline,[13–16] and lepromatous[8,13,15,17,18] leprosy patients. The time gap from onset/detection of both infections varied in reports from 2 months[17] to 15 years.[13] While most report that leprosy precedes TB, Agawal *et al.,*[17] Agnihotri *et al.,*[12] and Trindade *et al.*[10] report cases of TB preceding. Both type-I[10,14] and type-II[15,16] lepra reactions have also been reported.

On review of data from three leprosy referral centres in Hyderabad, India from 2000 to 2013, we have identified 3 cases of concomitant disease (Table 1). Two were sputum positive, pulmonary TB cases associated with lepromatous leprosy. One case was extra-pulmonary, CNS TB, confirmed with real time polymerase chain reaction (RT-PRC) of cerebrospinal fluid associated with lepromatous leprosy. All cases of leprosy had been confirmed by slit skin smear.

WHAT IS THE EPIDEMIOLOGICAL SIGNIFICANCE OF TB AND LEPROSY CO-INFECTION?

It was Fernandez, in 1939, who first proposed the suggestion that Bacillus Calmette-Guerin (BCG) vaccination may confer protection against leprosy. His observation that a large number of lepromin-negative children became positive for the protein following BCG

Table 1. Three cases of concomitant leprosy and tuberculosis infection identified on review of data from three leprosy referral centres in Hyderabad, India from 2000 to 2013

	Case 1	Case 2	Case 3
Demographics	18 YO Male Indian unemployed	38 YO Male Indian Privately employed	46 YO Male Indian Illiterate labourer
Leprosy or TB diagnosed first?	Leprosy	Leprosy	Leprosy
Leprosy type	Lepromatous	Lepromatous	Lepromatous
Lepra reaction type	(Silent Neuritis)	Type 2	No
Slit Skin Smear/Biopsy Confirmed?	Yes	Yes	Yes
Average bacillary index at diagnosis of leprosy	5·4	4·4	++
Average bacillary index at diagnosis of TB	4·8	2·8	++
Change in condition of leprosy during episode of concurrent Tuberculosis	Sensation in hands & feet and power in the hands deteriorated after previously improving whilst on MDT	No change in condition of leprosy during episode of TB	No change in condition of leprosy during episode of TB
Time between leprosy & TB diagnosis	9 months	3 years	11 months
How far into MDT was the patient diagnosed with TB?	9 months	Completed MDT (30 months)	11 months
Risk Factors for TB	? Steroids at time of TB diagnosis	? Steroids previously for ENL	No known risk factors
Pulmonary/Extra-pulmonary TB	Pulmonary	Extra-pulmonary (CNS)	Pulmonary
Confirmed TB?	Sputum Positive	RT-PCR of CSF	Sputum Positive
Previous history/family history/known contact for TB?	No	No – Screened before steroids were started	No

Key: TB = tuberculosis; YO = years old; MDT = multidrug therapy; ENL = erythema nodosum leprosum; CNS = central nervous system; PR-PCR = real time polymerase chain reaction; CSF = cereberal spinal fluid

vaccination led him to hypothesise that this may confer some protection against the disease.[23] More recently, several large, high level evidence studies have supported Fernandez's original observations from 75 years ago.[24–28] For example, Goulart *et al.* measured the relative risk of leprosy occurrence in household contacts ($n = 1{,}396$) in Brazil, an endemic region for the disease, over a 5 year period. Their results showed that having a BCG scar conferred a 98% (RR = 0·02) protection against MB leprosy forms compared to not having a BCG scar.[24] In 2007, Zodpey reported a meta-analysis in which they analysed 29 case-control, cohort and randomized control studies investigating the effectiveness of BCG vaccination in the prevention of leprosy.[29] The findings of this study strongly support the protective effect of BCG vaccine.[29]

The belief that there is a level of cross immunity provided to leprosy from exposure to other myocbacterial species, such as TB, was first described by Chaussinand in 1948. He observed that the prevalence of leprosy was inversely related to that of TB and proposed that prior TB exposure protected the individual against leprosy.[30] Lietman *et al.* further investigated this theory of cross immunity by modelling the elimination of leprosy from Western Europe.[22] They argued that leprosy was endemic in Western Europe from the 11th to 13th centuries. However, it nearly disappeared during the TB endemic of the 17th and 18th century.[31,32] Through mathematical modelling, the authors are able to conclude that TB could have played a key role in the elimination of leprosy from Western Europe providing that the basic reproduction rate of leprosy was relatively low.[22]

On the other hand, the co-existence of the two mycobacteria has been demonstrated in archaeological samples by Donoghue *et al.*[3] who identified DNA from both pathogens in the same samples from several sites around the world. These dated from the Roman period to the 13th century.[3] From these observations, the authors suggest that both socio-economic conditions and immune changes in multi-bacillary (MB) leprosy, led to an increased mortality in TB, leading to historical decline in leprosy. For example, in 1993, Glaziou *et al.* reported on leprosy and TB co-infected patients ($n = 275$) from institutions in French Polynesia between 1902 and 1930 (pre anti-microbial treatment). Overall mortality in this cohort was found to be 21%. Interestingly, there was a much greater mortality in MB compared to paucibacillary (PB) patients (13% vs. 4% $P = 0{\cdot}003$).[6] In fact, Hansen reported similar findings in Oslo in 1895, citing TB as the major cause of death in his leprosy subjects.[33]

It is hypothesized that, reduced cell mediated immunity plays a role in reactivation of latent TB or super-infection with TB in MB patients. Lepromatous leprosy patients have been demonstrated to mount a lower TNF-α response and have reduced inducible signalling molecules, such as chemokine ligand-2 (CCL-2).[13,34] This may explain the increased dissemination and growth of TB in MB disease. However, Trindade *et al.* recently investigated the cell mediated responses of two patients who were diagnosed with borderline leprosy (BL) and TB. They were unable to find any aberrant response of the IFN-γ/IL-12/23 axis on immunological evaluation.[10] As genetic susceptibility to mycobacterial disease is commonly found in this signalling pathway[35] this may warrant further longitudinal work to add power to any results surrounding this hypothesis.

Despite evidence to support this co-infection hypothesis, evidence cited from historical texts needs to be considered circumspectly because of the problems with diagnosis during these periods. There is also an element of bias because patients in institutions would likely be at a higher risk of developing TB and would also be on life-long treatment, as opposed to modern curative regimes (multi-drug therapy [MDT]), which are now available.

In 2013, Hohmann & Voss-Böhme used mathematical modelling to investigate the epidemiological outcomes of the co-infection hypothesis. Through this model, they showed that the disappearance of leprosy in certain parametric regions could be explained by co-infection. Their model is based upon the incidence of leprosy epidemics, which suggests that the basic reproductive number of leprosy is greater than one. Therefore this means that the historical decline of leprosy requires external influences upon it.[21] The authors argue that the Lietman *et al.* cross-immunity model, relies on the reproductive number of TB always being greater than that of leprosy.[22] Therefore, in severe leprosy endemics the cross-immunity hypothesis could not be used to explain declines in leprosy following these periods. However, in the co-infection hypothesis the increased severity of a leprosy endemic would make patients more susceptible to TB infection, potentially allowing an explanation for the elimination of leprosy in these regions.[21]

The authors caution the reader that cross–immunity and co–infection theories may not be exclusive and that both mechanisms may, in fact, reinforce the actions of one another.[21] However, in the co-infection hypothesis an immunological relationship is not assumed as increased susceptibility towards TB infection may result from a general immune response or social stressor. In the cross-immunity hypothesis an immunological relationship is critical. Therefore, the co-infection hypothesis can also explain the inverse relationship between the two organisms if cross-immunity is not sufficiently supported by immunological evidence in the future.[21] Further investigation of immunogenetic host factors which predispose to protection/resistance to concomitant infection may provide further insight into future novel therapeutic targets for susceptibility, prevention and treatment of infection with either organism.

DOES MULTI-DRUG THERAPY (MDT) POSE A RISK OF RIFAMPICIN RESISTANCE DEVELOPING IN UNDIAGNOSED TB CO-INFECTION?

Rifampicin is a key component of anti-tuberculosis chemotherapy.[36] It has been demonstrated that in the treatment of TB, rifamycin containing regimes are superior to those devoid of a rifamycin agent.[37] It was Kumar *et al.* in 1982 who postulated their concerns about avoiding monotherapy of undetected TB with rifampicin as a once monthly dose in MDT for leprosy. They feared that this may promote the development of rifampicin resistance of TB in concomitantly infected patients.[7]

In our reported case, TB was detected 9 months in to MB MDT treatment. Encouragingly, despite worries of rifamycin resistance, secondary to rifampicin monotherapy in MDT where TB is undetected,[7,16] all patients at our centres were successfully treated for TB with conventional category-I anti-TB chemotherapy. None of the cases have suffered relapses of TB since completing category-I treatment. It would have been beneficial to have obtained sputum sensitivities from these patients at the time of TB diagnosis to ensure sensitivity to rifampicin still remained. This is something which we are now considering implementing in all future cases, to allow monitoring for development of rifamycin resistance.

Despite these concerns, there currently are no reports of rifampicin resistance identified in co-infected patients. However, longitudinal studies are lacking and more vigilant monitoring of co-infected patients on diagnosis of TB for rifampicin resistance is required to be able to investigate this further. Although this may be an unlikely consequence of monthly rifampicin treatment in India, where our cases are based, it may be a greater concern in regions where leprosy patients take daily rifampicin, such as in the USA. It is important that rifampicin resistance is viewed in consideration of general anti-microbial resistance and not just in

isolation to leprosy resistance.[38] This view has also been echoed in the WHO regional director of South-East Asia in her vision statement[39] and raises the question of whether broader resistance screening is required in all concomitant infections during the course of leprosy treatment to further strengthen antimicrobial stewardship and prevention of resistance.

ARE STEROIDS A RISK FACTOR FOR THE DEVELOPMENT OF TB IN LEPROSY?

Although many risk factors for TB are known, including HIV infection, diabetes mellitus, transplant patients on immunosuppression and birth and travel in the developing world,[38] the use of steroids and development of TB is controversial. Jick *et al.* report an increased risk of TB in patients on steroids in their case-control study investigating the link in a rheumatology cohort in the United Kingdom.[40]

Sreeramareddy *et al.*[15] and Prasad *et al.*[16] have reported on co-infected patients who had been treated with steroids before diagnosis of TB. Agarwal *et al.* report the case of a renal transplant patient who had been taking multiple immunosuppressant drugs, including steroids, for several years.[17] However, major trials of steroid treatment in routine MDT for leprosy, such as the TRIPOD studies, have failed to identify development of TB in some 300 patients who were followed up for over 24 months.[41,42] However, these studies only treated patients with low doses of prednisolone (around 20 mg). Dosing used in routine clinics in India can often be greater than this and for longer periods of time. For example, two patients identified with co-infection in our report (cases 1 & 2) had been commenced on oral prednisolone at 40mg initially. In case 1, we identified the patient had been taking steroids for a period of 9 months. There was no previous history of TB or infected contacts. However, there is no evidence of any screening for latent TB prior to commencement of steroid & MDT treatment, so a temporal relationship is difficult to establish.

One weakness in the argument for steroids increasing the risk of developing TB is that a large number of leprosy patients (especially MB leprosy, who as discussed above may be more predisposed to TB co-infection) go on to develop lepra reactions, which require steroid treatment. Therefore, this means that there is a high rate of steroid prescribing in leprosy. For example, in a recent retrospective analysis of clinical characteristics of MB leprosy patients ($n = 730$) 54% developed lepra reactions.[43] One study reports that in a region of Africa with an ANCDR of 7·1 per 100,000 population, there was a 'steroids started rate' in one year of 1·26 per 100,000 population. Steroid treatment was for a minimum of 16 weeks to treat reactions per patient.[44] With an estimated ANCDR for co-infection of 0·019 per 100,000 patients (in India) the incidence of patients started on steroids is approximately 66 times greater than the estimated incidence of co-infection with both diseases. Despite this, longitudinal work would be required to identify any temporal relationship between steroids and TB development with active screening of patients before commencing treatment.

Conclusion

Despite the paucity of reports, infection with leprosy and tuberculosis does occur concomitantly. There is now a growing body of evidence to support the interaction of these two organisms historically to the point that we can begin to consider that TB may have been involved in the pre-MDT era decline in leprosy across Western Europe. On review of cases in the literature along with new epidemiological modelling of concomitant infection, further

work to characterise immunogenetic host factors may provide insight into future novel therapeutic targets for susceptibility, prevention and treatment of infection. We highlight how a greater understanding of the risk of development of rifampicin resistance, not only in the context of leprosy must be considered. Finally, work to further characterise whether there is a true temporal relationship between prolonged course, high dose steroid therapy and TB, as is associated with so many other immunosuppressive therapies is urgently required. The addition of data on these topics may help to improve future leprosy service provision as well as highlight the need to approach infection prevention and anti-microbial stewardship from a more holistic point of view. This will become integral as the augmentation of service provision between different specialist areas continues to increase over the coming years.

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Conflicts of interest

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