Letter in Response to Previous Publication

Letter to the editor regarding Association between asthma, rhinitis and atopic dermatitis with leprosy: A case-control study

Dear Editor,

We read the article Association between asthma, rhinitis, and atopic dermatitis with leprosy: A case-control study with great interest.[1] The authors hypothesise that theoretically, atopic individuals mount a Th2 response which would inhibit protective immunity against *Mycobacterium leprae*. They further analysed their cohort to demonstrate a 'significant and linear increase in the occurrence of leprosy with an increase in the number of atopic diseases'. We have some critical observations about the methodology and the inference drawn from the results.

While describing the Th1/Th2 paradigm in their basis for explaining interactions between leprosy and atopy, authors seem to have oversimplified the spectral aspects of a nuanced disease like leprosy and its associated reactional states. The cited supporting literature and data behind the polarisation of immune responses are more than two decades old.[2,3] The duality of Th1/Th2 responses in leprosy has been reconsidered with the identification of several new subsets of immune players and conversely, atopy has been studied beyond Th2 responses.[4,5] To say that atopics should have more leprosy and leprosy should have more atopy is credulous and lacks evidence-based scientific plausibility.

In the study design, a total of 333 cases and only 93 controls had been recruited. The case-to-control ratio is suboptimal, making one wary of the result interpretation. To screen for possible atopy, the International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire was employed which is again fraught with multiple confounders and false positives. For instance, a runny nose or congestion can potentially be a part of leprous infiltration of the nasal mucosa. Itchy skin, rash, or eczema may be a part of autonomic dysfunction due to leprosy or the lesions of leprosy themselves. Also, the ISAAC questionnaire used is actually meant for children less than 13 years of age, while the mean age of the present cohort was 46.8 years. Despite its validation in adolescents, it often underestimates asthma.[6] Extrapolating this questionnaire beyond childhood and adolescence questions its validity.

To establish the diagnosis of atopy, the screening questionnaire needs to be more specific and ideally, it should be confirmed by examination as well. Also, defining atopy as 'having symptoms of rhinitis, asthma or atopic dermatitis at any time in life' would potentially misclassify the majority of the population to be atopic, let alone leprosy patients with disease-related confounders. As per the study definition, any individual who ever had itchy skin lesions as per the patient's recall even for a day was liable to be considered as atopic. As perception about eczema is vague in the general population and more so in populations with low socioeconomic status, there is a very high probability that it was overestimated just based on the past 12 months recall.

In the study, the chi-square test or Fisher's exact test was used to assess statistical differences between atopy and leprosy, the former considered as exposure and the latter as an outcome. However, for the study to have sufficient power, the sample size should be large to accommodate for the prevalence of atopy. In the proof-of-concept study by Smith *et al.* quoted by the authors, 68% of leprosy patients had atopy while 59% of controls had atopy.[3] From their reference point as well, sample size calculations come out as almost 448 cases and controls. There is no explanation for the sample size chosen in the present study. Also, studies of associations between two dermatoses often resort to the use of odd's ratio (OR) as was done in a recent study, where leprosy was found to have a strong association with 14 different dermatoses, particularly Crohn's disease with an OR of 6.6 and highest odds of co-diagnosis with diabetes with an OR of 2.71.[7] Apart from this, the lepromatous spectrum which theoretically has the most Th2 polarisation showed 11% prevalence of atopic eczema, versus 10% in the tuberculoid spectrum in the study

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which somewhat contradicts the biological hypothesis of the authors.

The paper poses many pertinent questions, as to whether there is a strong link in literature or a potential research question as to whether atopy is associated with a chronic bacterial disease like leprosy. If so, this can have therapeutic repercussions. This raises the fundamental conundrum as to whether we start screening all our atopy cases for leprosy or vice versa. The practical connotations of this study need a valid, statistical, and evidence-backed backbone as the suggestion of atopy with leprosy is fraught with confounders.

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Author's reply

Dear Editor,

We appreciate the opportunity to respond to the letter to the editor[1] regarding some critical observations about the methodology and the inferences drawn from our results.[2]

First, the International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire is an accepted and validated instrument worldwide and the scientific literature has shown high sensitivity, specificity and positive predictive value for the epidemiological diagnosis of allergic diseases, and it is known for its good reproducibility and validity in previous studies and its reliability in telephone interviews.[3,4] The great advantage of ISAAC is that it allows the comparison of data between studies from around the world. Although initially designed for children and adolescents, it is possible to use ISAAC for adults as well.[3–5] Nevertheless, we know that this questionnaire evaluates symptoms related to allergic diseases and that it is not possible to be certain that all patients are truly atopic (allergic), and classifying allergic diseases based solely on questionnaire responses may not fully capture the complexity and heterogeneity of these conditions that are known to have various genotypes and phenotypes. To accurately characterise the atopic state, it would be necessary to confirm it with laboratory data, such as immunoglobulin E (IgE) levels. Therefore, we acknowledge the limitation of our study regarding the confirmation of the atopic status of the patients, since it is epidemiological in nature. We encourage new studies on the association between atopic diseases and leprosy that include laboratory data.

Regarding the sample size, it is important to note that we worked with a convenience sample of patients treated at the University Hospital of the Federal University of Sergipe. The number of leprosy patients is limited, even in an endemic

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