Letter in Response to Previous Publication

Serum lipocalin-2 levels in leprosy

Dear Editor,

We read with expectant interest the original article titled 'Serum lipocalin-2 levels are decreased in patients with leprosy' by Heba A. S. Bazid *et al*., which evaluated serum lipocalin-2 levels in leprosy patients and its relationship to the pathogenesis and prognosis of the disease.[1]

However, we found the article to be confusing and non-explanatory about certain points. Specifically, it was not clear from the manuscript the basis of classification of patients into multibacillary (MB) and paucibacillary (PB) forms of leprosy. The clinical picture has been described separately: with skin lesions and without skin lesions, with nerve involvement or without nerve involvement. No accepted/known classification of leprosy has labelled the disease according to the number of nerves involved.[2] Same confusion persists for labelling of a patient with epistaxis.

Descriptive details of the lesions do not mention the number of hypopigmented and erythematous macules, leading to ambiguity in classifying these patients into PB and MB categories. Despite this, the authors assertively categorise them into PB and MB, seemingly implying a distinct clinical presentation without any overlap between skin lesions or nerve involvement. However, it is important to consider that morphological variations such as nodular lesions or those with infiltration can indicate lepromatous leprosy (LL), histoid leprosy, or erythema nodosum leprosum (ENL). Similarly, nodules with ulcers may be observed in ENL, and these ulcers could also develop into trophic ulcers, further complicating the clinical picture.

The primary issue arises from the apparent confusion observed in correlating the levels of lipocalin-2 with MB and PB disease as well as with controls. Lipocalin-2 is a 25kDa acute phase protein generated by inflammation and produces its protective effect primarily through stimulation of neutrophils, antioxidant properties and as an iron scavenger, mostly related to infections with *E. coli*, salmonella, chlamydia and so on.[3] Higher levels of lipocalin-2 have also been reported in inflammatory chronic diseases due to neutrophil activation as in pustular psoriasis, hidradenitis suppurativa and more. For hidradenitis suppurativa, lipocalin-2 levels have been suggested even to be a blood marker for objective assessment of inflammatory activity.[4]

Thus, the cause-effect relationship of lipocalin-2 has to be explained in relation to leprosy; the levels should either be related to its preventive capability against infection or to the inflammation produced by infection with *M*ycobacterium *leprae*. In light of this available information, the findings are contradictory to the basic theory propounded that 'lipocalin-2 is a key component of the immune antimicrobial defense. So, if lipocalin-2 is protective, its levels should be higher in less severe and localised PB disease rather than in the more severe and widespread MB disease. If lipocalin-2 levels are related to inflammation produced by *M. leprae*, then its levels should be higher in patients – as they are in inflammatory diseases like pustular psoriasis, hidradenitis suppurativa and so on – than in healthy controls. The findings do not support either of the two suppositions.

The studies about the protective effect of lipocalin-2 in *M. tuberculosis* infection in extracellular culture in vitro have been ascribed to its capability to sequester iron.[5,6] While the role of lipocalin is established in other mycobacterial infections like *M. tuberculosis* and *M. bovis*, the implications of the same in leprosy has not yet been studied. Reference number 14 quoted by the authors have no mention about *M. leprae* either.[7] As neutrophils, oxidative damage and chelation of iron have a very insignificant role in the chronic course of infection caused by a very slowly dividing *M. leprae*, this may be a more valid reason for not studying the lipocalin-2 levels in various forms of leprosy.

The authors also mentioned the role of levels of lipocalin-2 in 'prognosis' of the disease, but did not amplify how this will work.

With the information provided, it is difficult to draw any worthwhile conclusions. We wish that the authors had addressed these issues to make the study more informative and more meaningful to the readers.

Declaration of patient consent

Patient's consent not required as there are no patients in this study.

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