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Editorial: Enhancing leprosy diagnosis: new tools and approaches for global health impact

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Editorial on the Research Topic
Enhancing leprosy diagnosis: new tools and approaches for global health impact

Leprosy is a critical neglected disease caused by *Mycobacterium leprae* and *Mycobacterium lepromatosis*, which is marked by a complex spectrum of clinical presentation (1). Despite being an ancient disease, there is a lack of laboratory tests that make leprosy diagnosis simpler, safer, faster, effective, and accessible, since the majority of cases of the disease are clustered in developing countries with economic and social internal heterogeneity (2). Late diagnosis remains a frequent occurrence, presenting high rates of new cases annually, especially in children, which reinforces that the bacillus transmission is active (3). Physical disabilities or permanent sequelae are other highlights of late diagnosis that directly impact the patient's quality of life and could cause even economic limitations, and social stigma (4).

This editorial brings together studies that recognize the inherent complexity of leprosy diagnosis and present innovative approaches with the potential to overcome current limitations. All studies, ranging from reports of unusual clinical cases to those involving molecular or immunological algorithms, underscore the scarcity of leprosy diagnoses, the importance of practical laboratory tools in high-endemicity contexts, and the lack of drug support to mitigate the damage caused by the disease's neural progression.

Chen et al. highlighted that health systems often overlook leprosy as an initial diagnostic consideration, particularly when patients do not present with its classic clinical manifestations and negative usual laboratory tests. These factors, when associated with a lack of a trained health team, make leprosy diagnosis more onerous. In the present study, patients sought medical care due to a persistent fever suggestive of infection; however, screening tests did not yield results consistent with any diagnostic hypothesis of illness, despite a cerebrospinal fluid (CSF) pathological investigation. Only after the hypothesis of leprosy, histopathological examination, and slit-skin smear analysis were *M. leprae*

confirmed. One interesting finding was that, when analyzing nucleic acid sequences through metagenomic next-generation sequencing (mNGS) on CSF, we observed that *M. leprae* may invade the CNS, possibly causing neurological complications.

The search for molecules capable of stimulating immune response in individuals with leprosy has been tested as possible targets for the development of diagnostic tools since 1980, when anti-phenolic glycolipid-I (PGL-I) was identified as an antibody specific to *M. leprae* (5). However, although serology contributes to the screening of leprosy cases even in endemic areas, there is still a significant limitation in the use of this tool as a diagnostic tool due to its limited sensitivity (6). Carvalho et al. associate the quantification of cellular immune response mediators with statistical tools and algorithmic methods to identify biomarkers that may be associated with leprosy and/or leprosy reactions and may help physicians in the diagnosis and prognosis of the disease. All biomarkers tested display an increase in immune cell mediators in leprosy patients compared to non-leprosy patients; however, CXCL10, CCL3, and CXCL8 chemokines, IFN-γ, and IL-6 pro-inflammatory cytokines, and IL-9 regulatory cytokine showed greater clinical relevance and possible applicability in the diagnosis of leprosy. Additionally, using classification tree, it was possible to categorize patients according to the combination of plasma concentrations of two or more of these selected biomarkers, being CXCL8 the parameter that showed the highest accuracy and significance in household contacts and CCL3 was the only analyte with moderate applicability to differentiate paucibacillary (PB) x multibacillary (MB) patients or PB x non-leprosy cases.

The complexity of leprosy diagnosis is even greater when there are no skin lesions and only neural manifestations are found (7). Diagnostic support through nerve biopsy analysis is an invasive and low-sensitivity approach to identify the bacillus (8). De Athaide et al., in a broader evaluation of this nerve sample, showed differential expression of genes linked to neuronal development, autophagy disruption, and immune responses, with inflammasome activation emerging as a key pathological feature. Linking the autophagy and inflammasome pathways to the mechanism of neural damage caused by the specific bacillus in the nerve provides the possibility of specific markers for the laboratory diagnosis of neural injury, as well as new evidence and opportunities for studying these pathways, which are still understudied in disease progression.

Studies testing alternatives of treatment are even rarer, especially when related to leprosy reactions, even though about 30%~50% of patients develop any symptoms before, during, or after multidrug therapy (MDT). One of these immune hyperactivities that could progress to physical disability and deformities is leprosy neuritis. Dos Santos et al. demonstrate the effectiveness of using intravenous methylprednisolone in both attack and maintenance applications. All evaluated nerves showed similar motor scores, similar to what is observed in traditional treatment using prednisone. Extensive nerve damage, as observed through electroneuromyographic studies, supports the irreversible sequelae of participants and the limitation of recovery. Although there is no clinical improvement with the use of intravenous methylprednisone, the lack of neural worsening supports the hypothesis that this treatment proposes a reduction in the oral dose of oral corticosteroids and, consequently, minimizes systemic side effects associated with long-term corticosteroid use.

Among the complications in the progression of leprosy, we can also mention treatment-related problems. Since the 1940s, dapsone has been one of the main antibiotics used in treatment. However, especially for Asian populations (9), there is great concern due to its potential for severe adverse reactions. Approximately 1.4% of patients (global prevalence) develop Dapsone Hypersensitivity Syndrome (DHS), which has a mortality rate of 9.9% (10). Due to its severity, early diagnosis is of great importance (11). In 2013, the HLA-B*13:01 allele was found to have a strong relationship with the development of DHS, present in a significant percentage of the Chinese population, but absent in Western populations (12). Menaldi et al., who found a strong relationship between this same allele in an Indonesian population, are essential to validate this genetic marker as a screening tool to identify individuals at high risk of DHS before starting dapsone, potentially improving management and preventing serious adverse events.

In summary, the development of new therapeutic regimens, diagnostic and monitoring platforms, and the application of new biomarkers are key strategies for subclinical and challenging diagnosis, preventing disabilities and halting the disease's spread.

Author contributions

AG: Data curation, Methodology, Conceptualization, Supervision, Validation, Writing – review & editing, Investigation, Software, Formal Analysis, Writing – original draft, Visualization, Resources, Funding acquisition, Project administration. NP: Writing – original draft, Resources, Investigation, Funding acquisition, Writing – review & editing, Project administration, Validation, Conceptualization, Visualization, Supervision, Formal Analysis, Methodology, Data curation, Software. FL: Conceptualization, Writing – original draft, Investigation, Resources, Visualization, Funding acquisition, Software, Project administration, Validation, Formal Analysis, Writing – review & editing, Methodology, Data curation, Supervision.

Conflict of interest

The authors declare that the editorial was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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