IJMPES International Journal of
Medical Parasitology & Epidemiology Sciences

http://ijmpes.com
doi 10.34172/ijmpes.2020.15
Vol. 1, No. 3, 2020, 42-44
eISSN 2766-6492

Editorial

Leprosy and Parasitic Coinfections

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Biosketch

During and after my study I worked as a human sports and cardiac physiologist at the Physiological Institute of the University of Utrecht but decided to contribute to this world by working in developing countries. That was a common decision for young people at that time. I left for Ethiopia with my family in 1974, where I worked as MD (leprology/dermatology), head of clinical research at the All Africa Leprosy and Rehabilitation Training (ALERT) center, during the communist revolution. I went to the hospital on horseback to do consultations at the Cheshire home for handicapped children at a distance of 15 km, on the other side of Addis Ababa. This was needed because of the surrounding of Addis by Cuban troops and farmers militia, it was near impossible to go directly through this controlled area.

In 1979, I returned to the Netherlands and started a residency to become a certified dermatologist. I did not stay long and soon after finishing my training became head of the Leprosy and Dermatology Program within the Ministry of Health of Zimbabwe in 1983. It was just after the freedom war that Mugabe started fighting (killing) the Ndebele opposition. We stayed there until 1986. Our family with young children needed to return to affordable schooling. Thus, after three years, we drove back with an old Landrover, man, wife, 3 children, and 2 dogs through the whole Africa to the Netherlands. I worked from 1986 to 1996 as the head of the Dermatology Outpatient Department of the Dijkzigt Hospital, predecessor of the Erasmus MC. I stayed true to my decision to work in the tropics, and from 1999 onwards I work twice a year for 3 months in low- and middle-income countries with a job at the IJsselmeer hospitals, and later with my own private practice. Just after the Iraq-Iran war, I visited Iran at the First International Leprosy Congress in Tehran together with Professor John Stanford, which left a good memory of the Iranian people.

I retired in 2013 but did not quit work completely. I have been home for one year due to Coronavirus pandemic, but before that I spent six to eight months per year abroad and teach doctors and students all over the world, from the United States to India and from China to Indonesia. In the Netherlands, I still train dermatologists, general practitioners, physiotherapists, infectious disease specialists, and residents of the Global Health Programs in dermatology during the Netherlands Course in Global Health and Tropical Medicine. I wrote over 250 articles (of which 108 on PubMed) and book chapters. For this work, I received a Royal award; appointed Knight in the Order of the Dutch Lion (Ridder in de Orde van de Nederlandse Leeuw) and received the Eijkman Medal from the Dutch Tropical Community and the Certificate of Appreciation of the International League of Dermatological Societies. I still participate in the training of dermatologists in Africa and Brazil on the Internet. Reviewing articles and advising the migrants and doctors working in developing countries on teledermatology is my favourite pastime.

Leprosy

Mycobacterium leprae and *Mycobacterium lepromatosis* are obligatory intracellular microorganisms that cause a disease called leprosy, one of the oldest known human diseases. The bacilli have adapted so well to the human cell due to the fact that they only need a minimal number of their own genes to survive, as their genome has become extremely short. As a result, currently, most people are genetically resistant to the disease and the bacilli do not enter their body or survive and then multiply in human's body. In these people, it is believed that the bacillus cannot manipulate the host cell to its own advantage to create a suitable environment for survival (1). Only about 20% of the population is susceptible to leprosy, an estimate based on serology, epidemiological data, and the influence of immunosuppression (HIV) (2,3). The common belief in the past was that the adaptive cell-mediated immune system (CMI) was responsible for resistance to leprosy. However, some are now of the opinion that the CMI only contributes for this 20% to the resistance and determines the clinical image and the damage.

Therefore, infection with *M. leprae/M. lepromatosis* usually does not lead to disease. Among the susceptible population (20%), the majority can develop sufficient immunity depending on genetic factors, the environment, and immunobiological history (3).

Protective factors include: (*a*) Vaccination with BCG or another mycobacterial vaccine (*M. vaccae, M. indicus pranii*, etc., (*b*) Having contact with antigenic determinants in the environment that enhances protection (4).

Received: June 3 2020, **Accepted**: August 9 2020, **ePublished**: October 17,2020

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Promoting factors include: (*a*) Living in an area with a high risk of infection with a large inoculum, (*b*) immunosuppression (5), (*c*) Being in contact with antigenic determinants that reduce resistance to *M. leprae/M. lepromatosis* (4).

As a result, at most a small percentage (less than 1%) of infected individuals develop clinical disease (1,2).

The introduction of multi-drug treatment in leprosy (1982) had a dramatic impact on the prevalence of the disease in the world and the incidence decreased due to a decrease in the infection pool. However, the incidence has remained the same in recent years and new patients are still being identified, including children. Further progress in combating leprosy is hampered by the lack of appropriate tools to address this persistence in transmission, incidence, and long-term consequences of the disease (6). In 2011, ILEP Board approved a research strategy to stimulate studies to improve and introduce new tools to prevent leprosy infection, improve patient care, and reduce the effects of the disease (6). One study could be to look at the host's co-infections and whether they occur more or less in leprosy patients than in non-leprosy patients living in the same area and under the same economic conditions and whether there is any impact on the clinical course (3).

This study focused on the concomitant parasitic infections occurring in leprosy.

Leishmaniasis

Leprosy and cutaneous/mucocutaneous leishmaniasis share the same characteristics. They are both caused by intracellular organisms and have similar spectral, clinical, and histopathological manifestations driven by the host's immune response. The similarities between the two can lead to diagnostic confusion, both in hypopigmented maculae (7), nodules, and plaques. Leishmaniasis can increase the severity of type 2 leprosy reactions (ENL), but the overall effect on disease expression is unclear (8). Even in regions endemic to both diseases, the detection of co-infected individuals is uncommon. The largest group was described by Barnetson and Bryceson in 1978 and included eight individuals from Ethiopia (9). Interestingly, these patients presented with different immunologically-based forms of leishmaniasis and leprosy. Borderline lepromatous (BL) leprosy, for example, can be associated with either localized leishmaniasis (demonstrating a preserved Th1 profile and cellular immunity to Leishmania) or anergic diffuse leishmaniasis (with a complete absence of a Th1 profile and cellular immunity to Leishmania antigens) (3,10). Reports of concomitant mucocutaneous leishmaniasis (associated with a strong cellular and inflammatory anti-Leishmania immune response) and lepromatous leprosy (anergic) (11), as well as post-kala-azar dermal leishmaniasis (cellular anergy) and BT leprosy (CMI present) (12), illustrate that the cellular immune responses against *M. leprae* and *Leishmania* are quite species-specific and may differ in degree in the same host (3,10).

Nevertheless, due to the long incubation period of leprosy, the host immune response elicited by *M. leprae* antigens through cytokine pattern and orchestration can interfere with leishmanial immunopathogenesis. As documented in a patient with lepromatous leprosy, interleukin 10 (IL-10) production may have elicited a regulatory response that contributed to the control of tissue damage, by decreasing the tumor necrosis factor alpha (TNF-α) of the concomitant mucosal leishmaniasis (10,13). Accordingly, the addition of IL-10 in vitro has been shown to reduce the production of TNF-α by the peripheral blood mononuclear cells of patients with mucosal leishmaniasis (14). Co-infection of leprosy with kala-azar is reported even more rarely, despite the high endemic rates of both diseases in India and Nepal (15). Bansal et al hypothesized that there is a cross-immunity between *Mycobacterium* and *Leishmania* infection, as both organisms affect macrophage function. They reported a patient in whom macular variant of post-kala azar dermal leishmaniasis (PKDL) ("low resistance") coexisted with "high resistance" borderline tuberculoid leprosy (12). A patient presented in Sao Paulo (Brazil) with subpolar lepromatous leprosy with co-infection of visceral leishmaniasis (VL). These clinical manifestations are considered to be the anergic pole of both diseases (Th2 response). In this patient, after treatment of the VL, PKDL developed. The patient developed papules with epithelioid granulomas, thus altering the immunological response to the hyperergic pole (Th1 response) of the *Leishmania* infection, but the patient remained at the Th2 pole of leprosy indicating that the immune defect was specific for each microorganism (3,8).

Intestinal Worm Infections

Helminths have been with humans from the beginning and have adapted to the human host and the human host to them. At the outset of the study on the influence of helminths on the host's immune system, their involvement with the host was thought to simply suppress T helper type 1 (Th1) cells while inducing T helper type 2 (Th2) cells (16). However, this hypothesis would only explain the observed effects on autoimmune diseases caused by Th1 cells. However, worms also regulate diseases caused by Th2, such as allergy and asthma. The author states that different parasitic worms suppress different Th types in different people, involving regulatory T (Treg) cells (17). This may be the result of epigenetic changes over time (18).

It has been observed that intestinal worms can protect against complications in leprosy; however, they can also cause, for example, type 2 leprosy reactions. *Strongyloides stercoralis* is a ubiquitous nematode which is common in tropical and subtropical regions. It is usually acquired when soil filariform larvae invade intact skin (10).

Disseminated disease has been well described in leprosy patients receiving systemic steroid therapy but it can be prevented by treatment prior to immunosuppression. As mentioned previously, helminth infections are believed to direct the immune response towards a Th2 profile and induce IL-10 production and the proliferation of regulatory T cells, leading to down-regulation of Th1 responses (19). There is some evidence that down-regulation of Th1 by helminthic co-infection may be related to the clinical presentation of leprosy, which is dependent on an effective Th1 immune response (10). Data shows that the presence of worms can indeed interfere with the course of leprosy, promoting the development of MB disease (10). Treatment of soil-transmitted helminth co-infection can be followed by leprosy reaction at diagnosis within a co-endemic population. This is likely due to immune reconstitution after deworming (20). In a study conducted in Indonesia, there were more helminth positives in MB leprosy compared to PB and in patients with T2R compared to patients without T2R (3,21).

Another parasitic infection, Scabies may be the result of the sequelae of leprosy. Scabies can become very severe due to the loss of sensation (Norwegian scabies) and infection of wounds and ulcers which may lead to sepsis with its consequences (3).

Conflict of Interests
None.

Ethical Issues
Not applicable.

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