Leprosy and HIV: an analysis

Naafs, B.

SUMMARY

After the introduction of HIV in the *community, the number of* patients with *tuberculosis increased. Many of the HIV iníected patients suffer from clinical tuberculosis.* Other *mycobacterial infections* too *have an increased incidence among* the *HIV infected* patients, *but not* so *leprosy.*

Many researchers have looked *into this observation, however with conflicting results. But a major increase* in leprosy *prevalence among HIV* infected *patients was* never *encountered, nor a significant increase oí HIV sero-prevalence among leprosy patients.*

In Africa during the past 30 years *a continuous fall in the leprosy incidence was seen. However in* recent years *the decline seems to* come to *a halt and in some areas* an *increase is observed.*

The author speculates that M.leprae does not cause clinical disease in already HIV infected patients, *since M.leprae is virtually non-toxic and needs a more or less functioning CMI to cause clinical disease. However the bacterium will multiply, the patient becoming a multibacillary carrier contributing to the infective mycobacterial* pool. *The non-HIV* infected *persons then have more chance* to *be infected and may develop clinical leprosy since they have a functioning CMI.*

The author thereíore *forecast an increase in leprosy incidence* over the *coming decade in countries, like Brazil, with endemic leprosy, where at present HIV íinds a foothold.*

Uniterms: Leprosy, HIV, Epidemiology.

'Ben Naaís MD PhD. dermatovenereologist
lisselmeerziekenhuizen Emmeloord/ Lelystad.

Consultant Tropical and Import Dermatology, Department of Dermatology
Leiden University Medical Centre (LUMC), Leiden, The Netherlands.

Visiting Lecturer Regional Dermatological Training Centre (RDTC) at the Kilimanjaro Christian Medical Centre (KCMC), Tumaini University, Moshi, Tanzania.

Correspondence to: Dr. B. Naaís, Gracht 15, 8485KN Munnekeburen, The Netherlands
E-mail: benaaís@dds.nl

INTRODUCTION

Human immunodeficiency virus (HIV) infection has altered the epidemiology of mycobacterial diseases15,27 It has led to an increase in severe illness associated with a number of mycobacterial diseases", those of the Mycobacterium avium intracellulare (MAIS) complex in the industrialised world and of tuberculosis (TB) in Sub-Saharan Africa. From there a more than doubling of the number of cases is reported[27,32].

The interaction between TB and HIV led the WHO to declare TB a global emergency.

A similar increase was expected for M.lepraet[21] It was also forecast, extrapolated from animal experiments; monkeys inoculated with the Simian immunodeficiency virus and M. leprae, that developed lepromatous disease, that the percentage of lepromatous patients among those infected with HIV would increase'". Indeed some epidemiological data show a small predilection for lepromatous leprosy[4,10] but most did not[18,19,31].

Analysing the presently available data[1,4,5,8,11,15,17,19,25] it appears that M. leprae behaves differently from M. tuberculosis. Most epidemiological studies did not show a difference in the HIV seroprevalence between leprosy patients and healthy controls. There was also no difference in the prevalence of leprosy in the HIV infected population compared with the non-HIV infected[19]. This is contrary to the situation seen in tuberculosis, where tuberculosis is more prevalent among HIV infected patients than among the non-HIV-infected population and the HIV seroprevalence is much higher among patients suffering from tuberculosis than among healthy controls[6,7,30,32]. How can such a difference be explained?

CONSIDERATIONS

Leprosy is an infectious disease caused by a virtually non-toxic bacterium, M. leprae. The disease presents with a clinical spectrum that seems to be determined by the Cell-Mediated Immunity (CMI)[3,23,28]. At one end of the spectrum is tuberculoid leprosy that presents with only a few, well-defined skin and nerve lesions. Tuberculoid leprosy is accompanied by a strong

CMI to M. leprae antigens. This has been shown using lymphocyte transformation tests (LTT) and macrophage inhibition tests (MIT)'. In histopathology is M. leprae not easily detectable.

Lepromatous leprosy represents the other end of the spectrum. The skin of the patient is diffusely infiltrated with bacteria. In later stadia infiltrated plaques and nodules may be seen. There are no signs of an active CMI, neither in vitro; M. leprae antigens do not elicit a reaction in LTT and MIT, nor in histopathology. It has been stated that there is no other human infection with such a perfect parasite-host relationship. The lepromatous patient provides the ideal culture medium. The bacteria multiply unharmed and the patient stays healthy with hardly any sign of the disease.

Between these two extremes most of the patients are classified in the borderline group. Patients with more tuberculoid features are classified as borderline tuberculoid (BT) and those with more lepromatous features as borderline lepromatous (BL). In between, a few mid borderline (BB) patients are classifie[23,28,29].

The duration of the incubation period has aroused some controversy. Extremes have been cited from 3 months to 60 years. The majority of the tuberculoid patients, however, seem to go through an incubation period of between 2-4 years, lepromatous patients through a "silent period" of at least 5-10 years. It seems that the less active the CMI, the less clinical symptoms are noted, the later the leprosy is diagnosed.

The acquired immunodeficiency syndrome (AIDS) is caused by a retrovirus, the human immuno-deficiency virus (HIV). The virus is especially bound to the CD4 receptor, which makes the CD4+ T cell a main target. It renders the cell functionally defective. When it is internalised and multiplies within the lymphocyte, the cell is destroyed. As result, during the course of an HIV infection the immune reactivity that is related to the CMI, slowly collapses. This can be shown with recall antigens both in vitro. using the LTT, and in vivo, using skin testing[16]

The exact incubation time is not known, the virus can be detected after 2 weeks - 12 months, depending on the initial viral load and on as yet unknown factors. The first signs of immunosuppression may be noted after 1-10 years or not at all.

When a patient acquires both the HIV and M. leprae, both infections may establish themselves. The HIV infection slowly destroys the CMI and M. leprae can therefore, at least theoretically, multiply unchecked.

It seems that M. leprae and M. tuberculosis are different in their "toxicity" to the human".". M. leprae does not cause an obvious response when inoculated in previously non-exposed individuals, but M. tuberculosis does, mobilising polymorphs, causing inflammation, infiltration and sometimes even ulceration. In tuberculosis, contrary to leprosy, the clinical features are not only caused by the CMI but by other inflammatory mediators as well,

Tuberculosis becomes manifest in an HIV infected patient when the compromised CMI is not able to control the bacterium. M. tuberculosis multiplies fast as compared with M. leprae. Moreover, as mentioned before, in tuberculosis also non-CMI related mechanisms contribute towards the clinical symptoms. Therefore, signs and symptoms may appear relative early[19] M. leprae multiplies very slowly", one division a fortnight and is not toxic, and needs, with polar lepromatous leprosy as an exception, a more or less functioning CMI to develop clinical disease. It has been stated that without the CMI there would be no leprosy[14]. Since during the course of an HIV infection the CMI declines, it may be expected that M. leprae infected HIV patients develop clinical leprosy only at the beginning of the HIV infection, when the immune system is still functional. It is likely that the clinical signs of leprosy will not develop later in the course of the HIV infection. When they nevertheless do develop, they may be inconspicuous as reported by Kennedy et al's. After 5-10 years if the patient survives it could be possible that leprosy manifest itself as polar lepromatous leprosy with an infiltrated skin, teeming with bacteria, hardly possible to diagnose and most likely one of the patients least problems. Leprosy in an HIV infected patient should be considered downgrading leprosy. Though a leprosy infected HIV patient may not develop clinical leprosy he will be infectious to others, spreading the bacteria, not only among the HIV- infected patients but also among the nonHIV-infected healthy population and those will develop clinical leprosy.

DISCUSSION

In some countries, together with an increase in the HIV seroprevalence, the incidence of tuberculosis which was previously declining is increasing again30 In contrast to the rise in incidence of tuberculosis, the incidence of leprosy continued to fall and was doing so for at least three decades. Until recently, it seemed that the incidence was falling even faster15. Some investigators contributed this to the success of leprosy control and especially to the introduction of MDT, others considered the improved socio-economic conditions to be responsible. Since it was shown that BCG is a good vaccine against leprosy, it became more fashionable to consider BCG vaccination to be the major factor for the decline in the detection rates22. There are however epidemiologists who are of the opinion that the observed fall in incidence is fully compatible

with the normal decline of an epidemic, no other explanation is needed.

In some countries the decline is levelling off since a few years or halting. In some East-African countries even an increase in the number of detected cases can be observed, which can not be explained by improved detection[24].

If it is true that leprosy infected HIV patients will become M. leprae carriers, contributing to the infectious pool of M. leprae, it can be expected that the healthy non- HIV infected individuals will be increasingly exposed to M. leprae. These then may develop leprosy, causing the incidence to increase.

There are a few papers that seem to contradict the above analysis. A report from Haiti that shows that relapse was more common among HIV seropositive than among HIV seronegative leprosy patients25. Pönnighaus observed the same trend in Malawi26. However, these findings can be explained by assuming that the relapsing patients, despite the HIV infection, had a functional immune reactivity against M. leprae antigens. Therefore, the clinical symptoms became detectable immediately after M. leprae started to multiply before the CMI had collapsed. Another explanation that may apply in future to similar observations is that in patients who receive anti-viral treatment the immune system recovers and recognises the

M. leprae antigenic determinants, causing clinical disease. Some HIV infected lepromatous patients may develop signs of ENL before other clinical symptoms of leprosy become visible, others may have more severe ENL when under antimycobacterial treatment. This can be explained by the observation, that in the beginning of an HIV infection, a polyclonal activation of B cells can be seen. The antibodies then formed may combine with M. leprae antigens to immunecomplexes and give rise to an ENL reaction.

There are two publications from Zambia in which it was claimed that neuritis and reactions were more serious in HIV infected than in HIV non-infected leprosy patients[20,33]. The occurrence of reversal reactions (Type 1 reactions) in HIV patients can be explained by the observation that in the beginning of an HIV infection, the CMI is still present, though unbalanced. Also some other immune mediated dermatoses may be observed at the beginning of an HIV infection, like alopecia areata, bullous eruptions, drug eruptions and psoriasis, but even other granulomatous diseases like granuloma annulare.

Further investigations have to be undertaken to elucidate the relationship between HIV and M. leprae infection. Therefore, other methods for the detection of a leprosy infection such as serology and polymerase chain reaction (PCR) should be developed further and used.

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