Mycobacterium ulcerans disease in West Africa
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Do environmental or genetic factors contribute to the risk of getting Buruli ulcer?

Buruli ulcer disease, caused by *Mycobacterium ulcerans*, is emerging in West Africa. After a brief introduction in chapter 1, a review of the clinical features of Buruli ulcer disease is given in chapter 2. It is assumed that a significant proportion of the population living in an endemic area - and exposed to *M. ulcerans* - never develop Buruli ulcer disease. Genetic or environmental factors explaining the development of Buruli ulcer disease once individuals have been infected with *M. ulcerans*, are discussed. The hypothesis that schistosomiasis is a risk factor for Buruli ulcer disease was based on the following considerations. In the years following the construction of the Akosombo dam in 1964, the prevalence of schistosomiasis has increased in areas around Lake Volta. In the same period Buruli ulcer disease emerged in the same areas. An increased helminthic infectious burden might conceivably cause a switch in the immune system in human hosts, i.e., changing the immune response pattern from a Th1 to a Th2 type, making them more susceptible for mycobacterial infection. Furthermore, possible genetic host susceptibility factors for Buruli ulcer that are relevant in other mycobacterial diseases are discussed.

Healing disease stages in Buruli ulcer may be accompanied by a protective (Th1 type) immune response, as was studied in chapter 3. A cellular Th-1-type immune response with high levels of gamma interferon (IFN-γ) is regarded as crucial for the host defence against mycobacteria, whereas interleukin-4 (IL-4), IL-5 suggest a Th-2-type immune response; and IL-10 suggest blunting of immune response now believed to be controlled by T regulatory cells. Of the 39 Buruli ulcer patients included, 23 patients were in the early disease stage, and 16 in the late disease stage. As controls, 39 healthy Ghanaian subjects participated. Early-stage Buruli ulcer patients produced significantly lower levels of IFN-γ and IFN-γ/IL-4 ratios compared to late-stage Buruli ulcer patients. IL-10 and IL-4 production did not differ between the disease stages. Although data were not collected with a longitudinal study design, the differences in IFN-γ/IL-4 production between early and late stages provide some evidence for improved immune function once healing occurs.

The hypothesis that schistosomiasis is a risk factor for Buruli ulcer was tested in chapter 4. Serum samples from confirmed Buruli ulcer patients and healthy controls were included in the study. The association between helminthic infections and Buruli ulcer was measured by detecting anti-schistosome antibodies. An increased antibody response in detection rate among Buruli ulcer patients compared to controls was found, suggesting a possible alternative or additional susceptibility to *M. ulcerans* infection by helminthic parasites.

In chapter 5, we investigated genetic susceptibility factors for Buruli ulcer because associations between infections, such as tuberculosis and HCV, with Buruli ulcer patients and controls have been described. Three single nucleotide polymorphisms, such as tumor necrosis factor (TNF), were associated with increased susceptibility to Buruli ulcer. One gene, one of which was *SLC11A1*, was found to be significantly associated with increased susceptibility. The association between gender, age, and risk of infection with *M. ulcerans* found by others, and the GG genotype found by us, lend support to an association of susceptibility with the *SLC11A1* gene in the population studied. The estimated 13% polymorphism was present among all genotypes.

Difficulties in diagnosis: Polymerase Chain Reaction

Laboratory confirmation of *M. ulcerans* was regarded as the "gold standard" for diagnosis. Several studies have shown promising results using *PCR* to detect *M. ulcerans*. This PCR was able to identify *M. ulcerans* in early case of Buruli ulcer patients and histopathological samples.
emerging in a review of the chapter 2. It is living in an Buruli ulcer development infected with somiasis is a wing consid- Le. Buruli ulcer emerged in areas are based in areas disease emerged burden might an hosts, i.e., a Th2 type, L infection, for Buruli are discussed. accompanied by a in chapter 3. Th2-type response are the 39 Buruli disease stage, Ghanaian produced sig- compared to did not dif- infected with a longitudinal study design, the differences in Th1-type cytokine production between early- and late-stage Buruli ulcer might reflect an improved immune defense over time.

The hypothesis on schistosomiasis as a risk factor for Buruli ulcer was tested in chapter 4. One hundred six out of 159 patients with confirmed Buruli ulcer and 106 matched community controls were included in the study, in which circulating anodic antigen was measured by detecting circulating anodic antigen in serum. No difference in detection rates and worm burden among patients and matched controls was found. These results do not support the hypothesis that susceptibility to Buruli ulcer is driven by a co-infection with schistosomes.

In chapter 5, we investigated the role of SLC11A1 (NRAMP1) in Buruli ulcer because of its associations with other mycobacterial infections, such as tuberculosis and leprosy. In total 182 Buruli ulcer patients and 191 healthy neighborhood-matched controls in Ghana were enrolled and tested for three polymorphisms in the SLC11A1 gene, one of which was the D543N. The D543N polymorphism was significantly associated with Buruli ulcer: the odds ratio (adjusted for gender, age, and region of the participant) of the GA genotype versus the GG genotype was 2.9 (95% CI: 1.41-5.91). These data lend support to a role in susceptibility of the polymorphism in the SLC11A1 gene in developing Buruli ulcer disease in Ghana, with an estimated 13% population attributable risk.

Difficulties in diagnosing Buruli ulcer: what can Polymerase Chain Reaction (PCR) add to solve this problem?

Laboratory confirmation of Buruli ulcer is complicated as no "gold standard" for diagnosis exists. A nested primer PCR based on IS2404 has shown promise as a diagnostic assay. In chapter 6, we evaluated this PCR to detect M. ulcerans DNA in tissue specimens from 143 Buruli ulcer patients in Ghana. Comparisons were made with culture and histopathology results. Of all 143 specimens, 107 (74.8%) showed
the presence of *M. ulcerans* DNA by PCR. Detection rates were influenced neither by the amount of tissue processed for PCR nor by the stage (pre-ulcerative or ulcerative) of disease. For future studies, small tissue samples, e.g., punch biopsy samples, might be sufficient for case confirmation. A letter to the Editor stressing the need of inclusion of Buruli ulcer disease in the differential diagnosis of ulcerative lesions is presented in chapter 7.

**Impact on daily life:**

Which cultural and religious factors determine how people deal with Buruli ulcer once they contract it? Which factors are associated with functional limitations and subsequent employment or schooling in Buruli ulcer patients? How can these functional limitations be evaluated? Are there differences in treatment outcome between hospitals?

The purpose of the study in chapter 8 was to explore the beliefs and attitudes of people in Ghana towards Buruli ulcer. Quantitative and qualitative data were obtained in Ghana by interviewing patients with this disease and control subjects. Common perceived causes were witchcraft and curses. Financial difficulties, fear of the mutilating aspects of surgery, and social stigma were the main reasons given for delay in obtaining treatment. Patients are reluctant to seek treatment outside their own community. The stigma of the disease is huge, and is strongly associated with the mysterious nature of the condition, the lack of knowledge about its mode of transmission, and the lack of proper treatment. Stigma scores were higher among unaffected respondents and in a less endemic location. Education on the disease, usually propagated for early case detection, might be useful in reducing stigma. Buruli ulcer disease can lead to scarring, calcification, and contractures with permanent disabilities. In chapter 9, 10 and 11 the development of a Buruli ulcer functional limitation score and its reliability and validity is discussed. In chapter 9, an impression of the number of functional limitations was obtained by measurement of a reduction in range of movement (goniometer). In all, 13 functional limitations were measured and a score was proposed. Clinical judgment; the item score chart; reliability and validity (BUFLS) questionnaire; functional impression and treatment outcome scores. To determine reliability and validity of the condition score was repeated in the same patient 2 weeks after the first assessment. The inter-observer and intra-class correlation of limitation scores measured 13 functional limitations higher than in the first measurement when the functional limitations score was lower. The BUFLS can be assessed at 6 months, 1 year, and 6 months in clinical trials of Buruli ulcer disease patients, and is associated with functional limitations and school dropout. Of the 132 patients, 20 had a functional limitation score of 0, allowing the treatment of female gender, and a persistent wound associated with the development of a functional limitation score for stopping occupation, financial difficulties, and school dropout.

A plea for rehabilitation from the functional limitations caused by Buruli ulcer disease.

Treatment effects...
Summary

A plea for rehabilitation programs is made to diminish the suffering from the functional limitations and employment or schooling problems caused by Buruli ulcer.

Treatment effects were assessed in chapter 13 by following up 78
patients treated for Buruli ulcer in two hospitals with different treatment aspects, including use of rifampicin, BCG vaccination status, and widely differing surgical practices. Of the 33 patients treated in hospital A, six (18%) were not healed at follow-up, whereas of the 45 patients treated in hospital B, 21 (47%) were not healed. The length of stay in hospital A was significantly longer, and more operations on average were done per patient. Using a logistic regression model for multivariate analysis, only treatment as given in hospital A, with standard practice of wide surgical excision, appeared to predict ulcer healing independently. This study shows large differences in treatment outcome between the two hospitals; the results support the hypothesis that extent of surgical treatment influences the chance of healing of Buruli ulcer. In chapter 14 the need to improve existing treatment options is discussed, with a plea to develop better (especially non-surgical) treatment strategies.