

Humoral immunity in Hansen's Disease

Part of the Master's thesis. Department of Rheumatology/Laboratory of Rheumatology Investigation - LIM-17, of the University Hospital of the College of Medicine of the Universidade de São Paulo. Partially funded by the Foundation for the Development of Rheumatology, Brazilian Society of Rheumatology (other funds) and Sandoz Laboratories - São Paulo, Brazil

For many years immune response in leprosy has been studied. Since 1960 several reports dealing with humoral immunity have been described in the literature. Different autoantibody rates occur in leprosy. There is an increase in the prevalence of autoantibodies in elderly patients with long standing disease, in lepromatous leprosy and in those with reactional states. The differences in rates among various studies are attributed to different methods and variations among patient samples concerning age, gender, polar forms, therapy and other elements. The prevalence of numerous antibodies, immune complexes, cryoglobulins and complement levels have been studied by many authors. This also highlights the importance of the more recent reviews of anti-*Mycobacterium leprae* glycolipid antibodies such as the anti-phenolic glycolipid-I antibodies in which titers are variable and depend on genetic factors.

UNITERMS: Antibodies. Hansen's Disease. Immunity. Cryoglobulins. Immune complexes. Complement.

INTRODUCTION

The activation of both humoral (46) and cellular (71) immunity has been detected in Hansen's Disease (17,18). Especially in the lepromatous form, the polyclonal activation of B-cells has been known since the 1960's by means of antibody detection and seric hypergammaglobulinemia and is considered to be due to the chronicity of the disease. On the other hand, specific antibodies against the mycobacteria (03,31,44), other

mycobacterial immunoglobulins (15) and autoantibodies have been described (20,21,23,27,38,51,61,67), as in other infectious diseases (01,10,11,26,30,37,42,43,50,60), and are important for analysis and diagnosis (57,58,65).

SPECIFIC ANTIBODIES

In 1982, Hunter et al. (44), chemically described a glycolipid from *Mycobacterium leprae* cultivated in armadillos. Later the same structure was found in infected human tissues. Through enzyme-linked immunosorbent assay (ELISA), it was shown that these antibodies were specific to the *M. leprae* infection (19,40) and that patients with tuberculosis and other mycobacterial infections did not show any reaction to this antigen. The false-positive rate was 3%, and lepromatous patients presented the most

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significant rates of these antibodies called anti-phenolic glycolipid-I antibodies (anti-PGL-I) (84). Due to the low presence of levels of anti-PGL-I in patients exposed to the ELISA test for this antibody, is not considered diagnostic (34) but has been considered useful for epidemiological studies, especially in endemic areas (19,75) and patients that have been in contact with leprosy.

Recent studies have shown that the scope and magnitude of antibodies produced by mice against certain mycobacterial proteins may vary greatly (16). In studies with *M. leprae*, it is believed that these different responses are influenced by genetic background. After inoculating mice with *M. leprae* sonicate and the recombinant 65kDa protein, differences in the number and structure of the recognized epitopes were noted, and the participation of non-H2 genes was demonstrated (04).

AUTOANTIBODIES

Among rabbits, bacterial immunization causes development of antigammaglobulins very similar to the rheumatoid factor (01). Late, anti-DNA antibodies may be found along with proliferative glomerulonephritis diagnosed during autopsy (25). However, in Hansen's Disease, the sole presence of these antibodies has not been related to any specific clinical manifestation, except when immune complex deposits occur. In 1966, Azevedo and Melo (06) recognized that the decrease in complement activation in reactional states of leprosy is due to the complement binding by the antigen-antibody complexes.

The autoantibodies in Hansen's Disease appear at different rates that vary according to the population studied, to the methods used and to the period in which they were carried out. Although some study groups have shown a higher prevalence of Hansen's Disease than in the control groups (62), several autoantibodies have been identified, among them anti-nuclear factors (11,14,54,64,82), rheumatoid factors (21,42,64,67,82), anti-tireoglobulin (12,52,64,82), anti-smooth muscle, anti-cardiolipin (28,36,39,79), anti-collagen I and II (53), as well as false positive syphilis reactions (35,52), that may indicate the presence of anti-phospholipid antibodies and/or a cross-reaction with the mycobacterial antigenic components.

The production of antibodies is more characteristic of the lepromatous form (23,52,64), demonstrated by high titers of gammaglobulin (02,03,73) especially in the reactional states, and can be detected also in patients in disease remission (82). An inverse relation between the

antibody and the cellular reactions has also been suggested (63). Long duration of disease, old age, and a history of recurring erythema nodosum leprosum (ENL) predispose the formation of autoantibodies in these patients (63).

In several studies (05,14,20,21,23,47,52,64,66,68), the detection of the rheumatoid factor ranges from zero (55) to 100% (28). Since the latex fixation test is more sensitive and less specific than the Waaler-Rose test, it can be assumed that this sensitivity could contribute to these differences in rate. In addition, in studies where the rates are very high, the number of patients studied is low (08). The identification of seric rheumatoid factor in leprosy patients occurs both in tuberculoid and lepromatous forms, although with a higher incidence in the latter (64). According to Pechclai et al. (64), rheumatoid factor titers can be low, depending on the population chosen. In hospitalized patients titers up to 1:5120 were found (21).

The production of seric factors very similar to rheumatoid factor can be stimulated by microorganisms (rabbit hyperimmunization with *Escherichia coli* and *Bacillus subtilis*) (01). No correlation was found with arthritis or rheumatoid disease in these subjects. It is known that rheumatoid factors were also detected in infections such as tuberculosis (83) and syphilis (60).

Antinuclear factors and L.E. cells were studied in leprosy patients as an attempt to diagnose a possible association with connective tissue diseases (74), since joint and skin manifestations may mimic several rheumatic symptoms. Similar to rheumatoid factor, the rates found (08,23,47) varied greatly, ranging from zero (55) to 29% (14,63). Although L.E. cells have been found (14,47,52) and leprosy patients with lupoid aspects have been reported (12) the association with systemic lupus erythematosus was not significant.

Autoantibodies reactive to native or denatured collagen type II were detected in the serum of 11 out of 20 patients with the lepromatous form in which antibody levels were significantly higher than those with rheumatoid disease; however, none of these patients had any signs of arthritis (24).

CIRCULATING IMMUNE COMPLEXES ^(22,69,70,85), CRYOGLOBULINS ⁽⁵²⁾ AND COMPLEMENT ⁽²²⁾

Although the presence of autoantibodies does not always mean pathogenicity, the presence of immune complexes in the tissues does suggest some participation in clinical manifestations (86)

The perivascular immune complexes seen in the dermis, and bound to soluble mycobacterial antigens were detected in patients with ENL, suggesting a possible role in its pathogenesis (56). Immune complexes have also been demonstrated in renal biopsies of leprosy patients (32) and related to a decrease in complement in these patients (09).

Patients with borderline leprosy in reaction showed circulating immune complexes (IgG and the C3 fraction), while in lepromatous leprosy immune complexes were formed by rheumatoid factor and IgM, especially in those patients with arthritis (59), anti-mycobacterial antibodies and cryoglobulins (13).

By using the C1q reaction method, immune complexes were also identified in the serum of the patients with the tuberculoid form, in contrast to previous studies that showed elevated immunocomplexes only during ENL Reaction (72). Seventy percent of the patients with the lepromatous form studied by Rojas-Espinosa et al. (72) and 76% of the patients studied by Moran et al. (56) showed circulating immune complexes when the same method was employed.

Complement detection may be useful to the diagnosis of Hansen's Disease (48,76,77,81). High levels of complement, especially of the C2 and C3 components (33) during ENL episodes have been reported (78). Titers of complement in the synovial fluid may have a practical significance when compared to blood levels (49).

Cryoglobulinemia may cause severe complications such as proliferative glomerulonephritis with linear IgG and IgM deposits and granular deposits of C3 (45). A high frequency was observed during ENL, in patients undergoing treatment (58%) and in untreated patients with ENL (52). All six patients assessed by Bonomo (13) presented mixed cryoglobulins and IgG and five have polyclonal IgM, with one IgM presenting only light-chain kappa.

Although it is generally agreed that competent immunity for bacillar destruction is mediated by an efficient T-cell response, some authors emphasize the importance of specific immunoglobulins (29) in mucosal and in patients with lesser severity of the disease (40)

Humoral abnormalities are therefore important, particularly to differential diagnosis.

RESUMO

Introdução: Desde a década de 60, tem-se observado alterações da imunidade humoral na hanseníase. Os auto-anticorpos apresentam-se em freqüências diversas, nestes pacientes, mais habitualmente na hanseníase virchoviana, em doença de longa evolução e em surtos reacionais. Variação nas freqüências pode se atribuída a diferentes metodologias empregadas na detecção dos anticorpos e ao grupo de doentes selecionado. **Material e Métodos:** Esta revisão enfoca os resultados obtidos em diversos estudos de auto-anticorpos, complexos imunes, crioglobulinas, complemento sérico na hanseníase. Destaca-se também, os anticorpos contra glicolípídeos do *Mycobacterium leprae*, como os antiglicolípídeos fenólicos I, cuja magnitude é variável e depende do patrimônio genético apresentado pelo enfermo.

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