Increased incidence of HL-A 1 and 8 in patients showing IgG or complement coating on their red cells

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SYNOPSIS The incidence of HL-A antigens in patients having a variety of medical conditions, but sharing the common feature of a positive antiglobulin test of the red cells, was determined. There was a significant increase in the antigens HL-A 1 and HL-A 8 and of the 1 and 8 combination when compared with a control group. It is suggested that the presence of these antigens may predispose to autoallergy.

Recent reports in the literature have drawn attention to an increased incidence of the HL-A 8 histocompatibility antigen in several diseases, eg, systemic lupus erythematosus (Grumet, Coukell, Bodmer, Bodmer, and McDevitt, 1971), dermatitis herpetiformis (Katz, Falchuk, Dahl, Rogentine, and Strober, 1972; White, Barnetson, da Costa, and McClelland, 1973), gluten enteropathy (Falchuk, Rogentine, and Strober, 1972; Stokes, Asquith, Holmes, Mackintosh, and Cooke, 1972), chronic autoimmune hepatitis (Mackay and Morris, 1972), and myasthenia gravis (Fritze, Herrmann, Smith, and Walford, 1973). Often this increase is accompanied by a significant increase in HL-A 1. All these conditions have immunological undertones and are often associated with the production of autoantibodies. To test the hypothesis that the presence of these antigens either singly or in combination may predispose, or be an indicator of susceptibility to immune derangement, we considered that it might be interesting to study a group of people suffering from a wide variety of medical conditions sharing the common feature of Coombs positivity of the red cells. It is increasingly recognized that this occurs as a non-specific indicator of immune disorder.

Patients and Methods

Fifteen millilitres of defibrinated blood was obtained from 56 unrelated patients found to be direct Coombs positive either by specific testing or at grouping and cross-matching. The patients' diagnoses covered a wide spectrum of clinical disease. Twelve patients had idiopathic autoimmune haemolytic anaemia, 10 were taking methyldopa, nine had an underlying lymphoreticular disorder, 20 had a variety of conditions in which circulating immune complexes are likely to occur, eg, serum hepatitis, pernicious anaemia, paraproteinaemia, dermatitis herpetiformis, chronic renal failure, systemic lupus, scleroderma, and carcinoma. Five had positive Coombs tests without an obvious diagnosis. Of the 56 patients, 32 had haematological findings suggesting active haemolysis at the time of Coombs testing.

As normal controls, 613 blood donors from the same catchment area were HL-A typed all of them being direct Coombs negative. Screening for, and titration of Coombs-positive red cells, was done using polyvalent antihuman globulin. Cells found positive on screening were further tested with monospecific anti-IgG sera and an anticomplement serum prepared locally by injection into rabbits of autologous red cells pretreated with horse serum and zymosan-treated fresh human serum (Mollison, 1972). The specificity of the antisera was tested against panels of uncoated red cells, anti-Rh-coated red cells, and complement-coated red cells prepared by incubation with (a) normal incomplete cold antibody, (b) anti I, (c) anti-i, and (d) anti-Lea. In addition sera from all patients were screened for red cell autoantibodies using saline, cysteine papain, and indirect Coombs techniques.

HL-A typing was performed using a modified Teraski lymphocytotoxicity test. Lymphocytes were separated from defibrinated blood on a ficoll trisoli
gradient and tested against three antisera to each of the main histocompatibility antigens.

Results

The incidence of the major HL-A antigens in both patients and controls is shown in Table 1 where it can be seen that HL-A 1 and HL-A 8 both alone and in combination are significantly (p < 0.01) increased in the patient group, using the Yates corrected chi-square test and with a correction for Bonferroni inequality (Miller, 1966). This correction reduces sampling problems by multiplying the chi-square value for probability by the numbers of antigens tested (17). This increase is a property of all Coombs-positive cells irrespective of their coating substance and is seen equally well in patients with IgG alone or complement-coated cells, as can be seen from Table I, which also compares subgroups of patients sharing various common serological or clinical features.

No difference is demonstrable between patients whose serum contained warm autoantibodies and those with cold antibodies or a positive anti-complement Coombs test on its own.

Although the numbers are small, the frequency of the HL-A 1 and 8 combination in those classified as induced by methyl dopa approximated more to the level of the control groups than to any of the other patient categories.

With grouping on clinical grounds a slightly higher incidence of HL-A 1 and 8 is noted in those patients with clinical haemolysis, but no differences are distinguishable between those with idiopathic and acquired disease.

Discussion

Coombs positivity may occur in the presence or absence of red cell destruction. In the first instance haemolysis is due to cytolytic IgM or IgG red cell autoantibodies representing a type II hypersensitivity reaction. In the absence of haemolysis, Coombs positivity is often seen in relation to a number of disorders characterized by circulating immune complexes (type III hypersensitivity), which probably bind complement non-specifically to red cells during transient and reversible periods of immune complex/red cell interaction. Our findings indicate that HL-A 1 and 8 are increased in both these types of reaction involving red cells, irrespective of the underlying immunological derangement.

The low incidence of the HL-A 1 and 8 combination in the methyl dopa group is worthy of comment. It would suggest that the mechanism behind the Coombs positivity in this category is different to that appertaining in the other patient groups. Independent support for this suggestion is offered by a recent report demonstrating different physico-chemical characteristics for the panhaemagglutinins arising from therapy with this drug (Wenz and Lalezari, 1973).

The fact that HL-A 8 has now been associated with a variety of autoallergic diseases (Grumet et al., 1971; Falchuk et al., 1972; Katz et al., 1972; Mackay and Morris, 1972; Stokes et al., 1972; Fritze et al., 1972),
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1973; White et al, 1973) would tend to militate against the explanation that there is an aetiologial agent responsible for all these conditions which by 'molecular mimicry' to the histocompatibility antigen does not stimulate an immune response. A similar objection can be made to the suggestion that the HL-A 8 histocompatibility antigen represents a specific receptor site for the attachment of a pathogenic virus or other agent. A more feasible explanation would be that this histocompatibility antigen is in some way associated with a predisposition to some autoimmune diseases moderated possibly by a defective immune response gene. This is substantiated by the present studies which represent a heterogenous assembly of conditions that have the common feature of a 'forbidden' antibody to the red cells.

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References


