DISBALANCE OF IMMUNOGLOBULINS

THE CLINICAL IMPORTANCE OF INCREASED SERUM LEVELS OF IMMUNOGLOBULIN-A AND -G IN COMBINATION WITH NORMAL OR DIMINISHED IMMUNOGLOBULIN-M CONCENTRATIONS

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SUMMARY

A disbalance of immunoglobulin-A (IgA), immunoglobulin-G (IgG) and immunoglobulin-M (IgM) concentrations—*i.e.*, increased IgA and IgG fractions and a normal or diminished IgM concentration—is not a specific finding but one that frequently occurs in collagen diseases which take a chronic course. In the series studied, no correlation was demonstrable between this disbalance and the results of serological tests for rheumatic disease.

Chronic infectious diseases, auto-immune diseases, etc., are frequently associated with abnormalities in the composition of serum proteins[1]. The vast majority of cases show a polyclonal gammapathy[2,3], manifested in serum electrophoresis as a diffuse increase of the γ-globulin fraction. Immunoelectrophoretic analysis generally discloses an increase of immunoglobulins G, A and M (ref. 4)**.

Routine analyses in our laboratory of the immunoelectrophoretic diagrams of 1200 sera revealed that, in 55 sera, a normal or often even diminished IgM concentration was accompanied by a diffuse (polyclonal) increase of the IgA and IgG fractions. In view of this disbalance between the normal or diminished IgM and the increased IgA and IgG fractions, we decided to study the case histories of the patients concerned. Clinical data sufficient for further analysis were available on 22 of these patients. The object of this study was to establish whether a relation existed between this immunoglobulin disbalance and the diseases from which the patients were suffering.

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** Since data on immunoglobulin-D are still incomplete, this immunoglobulin was not taken into account.

MATERIAL AND METHODS

Sera from 1200 patients were examined with the aid of agar gel electrophoresis and immunoelectrophoresis.

The Wieme[5] micromethod was used in agar electrophoresis, and the Scheidegger[6] micromethod in immunoelectrophoresis. The antisera used were: horse anti-human serum (Central Laboratory of the Blood Transfusion Service, Amsterdam); anti-IgM prepared in rabbits against a purified pathological macroglobulin; anti-IgA prepared in rabbits against a purified pathological A-myeloma protein.

The immunoglobulins were not determined quantitatively but, during evaluation of the immunoelectrophoretic diagrams, estimated by comparison with a control serum made up of sera from 6 normal subjects.

RESULTS

As we pointed out in the introduction, immunoglobulin disbalance was found in 55 of the 1200 sera examined. Only from 22 patients were sufficient data available for further analysis. As a result of this selection of material, each of these 22 patients showed increased serum IgA and IgG fractions. A normal-to-slightly-diminished IgM level was demonstrable in 11 of the sera, while the remaining 11 sera showed a distinctly diminished IgM fraction (Fig. 1). The diagnoses in these 22 patients are presented

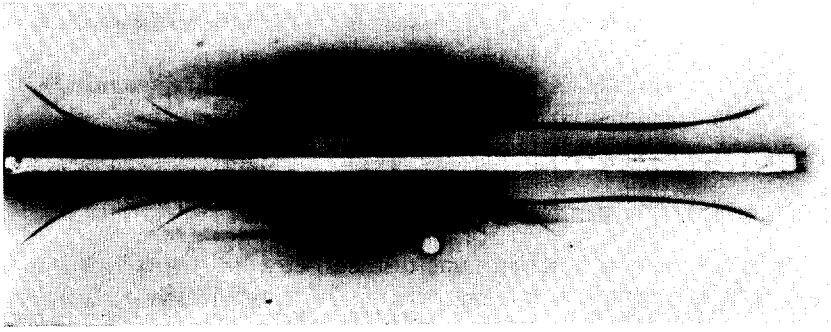

Fig. 1. Immunoelectrophoretic pattern of the serum of a patient with immunoglobulin disbalance (upper part) compared with that of a normal reference serum. Note the increase in IgA and IgG, and the decrease in the IgM level in the patients serum.

in Table I. Careful analysis of the remaining clinical and laboratory data disclosed no abnormalities other than those characteristic of the diseases from which these patients suffered. No distinct correlation was found between the immunoglobulin disbalance and any given clinical syndrome or any given laboratory or radiological abnormalities. One striking feature was, however, that 13 of the 22 patients were suffering from a collagen disease.

For reasons to be presented in the discussion, it was considered desirable to carry out a supplemental study in view of these results. Sera from an additional group of 17 patients with rheumatoid arthritis (stage III) were examined by agar gel electrophoresis and immunoelectrophoresis.

The R.A. test was negative in 7, and positive in 10 patients. All patients showed

an increased ESR. The immunoelectrophoretic examination of the sera from these patients revealed that the IgM level was normal or slightly diminished in 13 cases, and greatly diminished in the remaining 4 sera. In nearly all cases an increase in the IgG and IgA levels was found.

DISCUSSION

Immunoelectrophoretic examination of sera from 22 patients disclosed increased IgA and IgG fractions accompanied by a normal or often even diminished IgM concentration. The data presented in Table I indicate that this disbalance of

TABLE I

DIAGNOSES MADE ON 22 PATIENTS WITH IMMUNOGLOBULIN DISBALANCE

Collagen diseases:		13
Rheumatic fever	1	
Rheumatoid arthritis	12	
Neoplasms:		4
Pavement-cell carcinoma of the lung	2	
Thyroid adenoma	1	
Adenomatous polyp of the colon	1	
Diabetes mellitus:		2
With hyperparathyroidism	1	
With Boeck's sarcoid	1	
Chronic lymphatic leukaemia		1
Cirrhosis of the liver		1
Staphylococcal sepsis		1

immunoglobulins—even if differentiated by supplemental data on the albumin, α_1 AT-globulin, haptoglobin and transferrin concentrations—is not specific of any given clinical condition. This finding fully corroborates the conclusion formulated by Fahey[1] in a recent publication: "The immunoglobulin changes may vary widely in different patients with the same type of disease. Thus, the serum immunoglobulin levels are influenced by other factors, in addition to a specific pathological process". This conclusion is clearly illustrated by a patient in our series, with chronic lymphatic leukaemia—as, in most cases, this condition is associated with low levels of all immunoglobulins. Our series is conspicuous in that it includes a large number of patients with collagen diseases, which are usually described as accompanied by increased levels of all immunoglobulins[1,7,8]. Heremans[9] found that the three immunoglobulin fractions were nearly always increased in rheumatoid arthritis, whereas in rheumatic fever only 5 of the 12 patients examined showed an unequivocal increase of the IgM concentration. Discrepant results were reported by Comoli and Allegra[10], who carried out serum immunoelectrophoresis in 17 cases of rheumatoid arthritis. They found a strikingly low IgM level, polyclonal increase of the IgG fraction and a normal IgA fraction.

In 1963, Krebs and coll.[11] presented the results of an immunoelectrophoretic study in patients with psoriasis arthropathica and rheumatoid arthritis. A diminished IgM concentration was found in 12 of the 20 patients with psoriasis rathropathica. 9 of the 20 patients with serologically positive rheumatoid arthritis, however, showed an increased IgM fraction. Our findings contradict those of Peetoom, Fahey and

others, but are in agreement with those of Comoli and Allegra (although in our cases an increased IgA fraction was found in addition). Our patients were not suffering from psoriasis arthropathica. The fact that the rheumatic factor is a macroglobulin raises the question whether a difference in serum IgM level existed between patients suffering from rheumatoid arthritis who showed a positive R.A.-test and those with a negative R.A.-test.

It was in the context of this question that a supplemental study was carried out: sera from 17 patients with stage III of rheumatoid arthritis were submitted to immunoelectrophoretic analysis. The R.A.-test was negative in 7 and positive in 10 of these patients. In all cases, the IgM concentration was found to be normal or even diminished (in 4 cases greatly decreased). In no serum in this series was an increased IgM fraction found. Increased IgA and IgG values were found in 10 of these 17 patients.

These findings would seem to warrant the conclusion that rheumatoid arthritis is generally associated with a normal or diminished IgM concentration and, in many cases, with an increase of the IgA and IgG fractions.

This disbalance of immunoglobulins does not correlate with the rheumatic serology and is not specific of collagen diseases.

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