Multiple immunological abnormalities in a family

ALASTAIR M. S. MASON¹ AND PETER L. GOLDING²

From Southampton General Hospital and the London Hospital, London

SYNOPSIS The family of a woman with multiple autoimmune diseases has been investigated. Clinical evidence of an autoimmune disorder was detected in two relatives, and five others had serological and immunoglobulin abnormalities. It is suggested that there is an inherited predisposition to develop immunological abnormalities, and that a number of associated autoimmune diseases may develop in families in which this occurs.

Family studies on the non-organ specific autoimmune diseases have for the most part been confined to disseminated lupus erythematosus and rheumatoid arthritis. There is evidence that heredity may play a part in the pathogenesis of both disorders (Lawrence, 1965; Leonhardt, 1967).

There are isolated reports that an inherited immunological defect is involved in other disorders associated with hyperglobulinaemia and non-organ specific antibodies such as Sjögren's syndrome (Bloch, Buchanan, Wohl, and Bunim, 1965), renal tubular acidosis (Wilson, Williams, and Tobian, 1967), and diffuse pulmonary fibrosis (Bonanni, Frymoyer, and Jacox, 1965). No study in which the members of a family have been investigated for a number of these disorders has been reported previously.

We have investigated the family of a woman with multiple autoimmune disorders. All the relatives were screened for the presence of serological and immunoglobulin abnormalities. Those members with an abnormality were investigated for the presence of Sjögren's syndrome, renal tubular acidosis, liver disease, pulmonary fibrosis, hyperglobulinaemic purpura, peripheral neuropathy, and autoimmune thyroid disease.

Methods

All the living members of the family were examined, and blood was taken for plasma protein electrophoresis and for a series of tests for autoantibodies. Those relatives with hyperglobulinaemia as shown on the electrophoretic strip or with an autoantibody in

the serum were investigated as follows: blood urea, electrolyte, bilirubin, alkaline phosphatase, SGOT, and protein-bound iodine concentrations; the 45-minute retention of bromsulphalein; the ammonium chloride load test of Wrong and Davies (1959); the Schirmer and Rose Bengal tests with slit lamp examination of the eyes; and a chest radiograph.

Rheumatoid factor was detected by the slide test, Rheumatex (Colab Laboratories, Chicago, Illinois), and by sheep cell agglutination (Ball, 1950). Immunofluorescent studies were performed with a 1:10 dilution of the patient's serum by the method of Coons and Kaplan (1950). Autoimmune complement-fixation tests were carried out in a MRC pattern perspex plate using the method of Osler, Strauss, and Mayer (1952). Thyroglobulin tanned red cell haemagglutination was measured by the method of Fulthorpe, Roitt, Doniach, and Couchman (1961).

Serum immunoglobulins IgG, IgA, IgM were measured quantitatively by single radial immunodiffusion on an Immunoplate using the standards supplied by the manufacturer (Baxter Co, Thetford). The normal range of the IgG fraction was 600-1,200 mg/100 ml, IgA 170-410 mg/100 ml, and IgM 50-110 mg/100 ml.

Case Histories

The clinical details of the proband (S.S.) have been reported previously (Mason and Golding, 1970a). She presented, aged 57, with the 'sicca complex' and myxoedema. Four years later she developed renal tubular acidosis, hyperglobulinaemic purpura, diffuse interstitial pulmonary fibrosis, and a severe sensory-motor neuropathy.

Seven of the 19 relatives seen had an abnormality detected in the screening tests. The investigations

¹Present address: Clinical Research Centre, Northwick Park Hospital, Harrow, Middlesex.

²Present address: The Division of Medicine, the London Hospital.

Received for publication 18 February 1971.

described previously were performed on all seven subjects and unless stated in the case histories the results of these tests were normal.

E.B. is the non-identical twin sister of the proband. She had a long history of obstructive airways disease. The liver and spleen were enlarged. The serum bilirubin was 1.6 mg/100 ml, bromsulphalein retention at 45 minutes was 15%, but the other liver function tests were normal. A liver biopsy showed fibrosis of the portal tracts with a sparse infiltrate of lymphocytes, changes compatible with a diagnosis of autoimmune hepatitis.

A.L. was found to have the 'sicca complex' form of Sjögren's syndrome. Both parotid glands were enlarged and there was a marked reduction in the salivary flow rate.

P.B. had a subarachnoid haemorrhage aged 22 and now has a residual left hemiparesis. During the last five years she has been frequently admitted as an psychiatric patient and has been diagnosed as having schizophrenia.

H.H., E.H., V.P., and M.C. were all clinically well, and no abnormalities were detected on physical examination nor during the extensive laboratory investigation.

The family pedigree is shown in the Figure. The results of the immunological investigations in the eight relatives with immunological abnormalities are summarized in the Table. The serum IgG fraction was raised in four subjects, IgA in two, and IgM was raised in two but decreased in three. Rheumatoid factor was present in two, an antinuclear antibody in three, and smooth muscle antibody in one subject. A biological false positive Wassermann reaction and a positive Coombs test were detected in one relative.

FIG. 1. THE FAMILY PEDIGREE

Fig. 1 The pedigree of the family

Autoimmune complement-fixation tests were positive in three and an elevated titre of thyroid antibodies was detected in six subjects, two of whom had very high thyroid antibody titres. The 12 other members of the family had no autoantibodies in the serum and a normal protein electrophoretic strip.

Discussion

Investigation of the proband S.S. showed that she had multiple clinical syndromes. Four of them, the 'sicca complex,' purpura, renal tubular acidosis, and diffuse interstitial pulmonary fibrosis are frequently associated with hyperglobulinaemia and non-organ specific autoantibodies (Mason and Golding, 1970b). Myxoedema may occur with hyperglobulinaemia but is usually associated with organ specific autoantibodies. A peripheral neuropathy has been recorded as occurring with non-organ specific autoimmune diseases such as Sjögren's syndrome (Kaltreider and Talal, 1969; Mason and Golding,

	Subject							
	S.S.	H.H.	E.B.	A.L.	E.H.	P.B.	V.P.	M.C.
Sex	F	M	F	F	M	F	F	F
Age	65	64	65	57	56	29	38	34
Immunoglobulins								
IgG (mg/100 ml)	2,200	1,100	1,450	610	1,600	960	1,150	1,300
IgA (mg/100 ml)	410	300	570	235	390	500	160	180
IgM (mg/100 ml)	70	38	115	35	80	125	26	64
Autoantibodies								
Wassermann reaction	-	-	-	-	-	+	-	-
Coombs test	-	-	-	-	-	+	-	-
Rheumatoid screen	+	-	+	-	-	-	-	-
Sheep cell agglutination test	-	-	1/80	-	-	-	-	-
Antinuclear antibody	+++	++	-	-	-	-	-	++++
Smooth muscle antibody	-	-	++++	-	-	-	-	-
Mitochondrial a/b	-	-	-	-	-	-	-	-
Autoimmune complement-fixation tests	1/10	-	1/40	1/80	-	-	-	-
Thyroglobulin TRC	1/80	-	1/40	1/80	1/160	-	1/10000	1/10000

Table Summary of immunological investigations in eight members of a family¹

¹The 12 other relatives investigated had normal protein electrophoretic strips and none of the autoantibodies outlined above were present in the serum.

1970b). The concurrence of all six disorders in the same patient is apparently unique. Seven of the 19 relatives screened had both an abnormality of the immunoglobulins and autoantibodies present in the serum. They were systematically investigated but only two, the sisters E.B. and A.L., had clinical evidence of an autoimmune disease.

There was no consistent pattern in the immunological abnormalities detected in this family, but it is of interest that three relatives had low levels of serum IgM and only one of them had overt clinical disease (A.L.). It is probable that the deficiency of serum IgM is genetically determined but its occurrence as a secondary phenomenon cannot be excluded.

The role of heredity in the non-organ specific autoimmune diseases has only been fully studied in disseminated lupus erythematosus and rheumatoid arthritis. Leonhardt (1967), summarizing the evidence from his own studies and that of other workers, suggested that there is an inherited predisposition to disseminated lupus erythematosus. The position in rheumatoid arthritis is less convincing, and Lawrence (1965) considered that heredity may only play a part in the pathogenesis of chronic arthritis.

The other disorders associated with hyperglobulinaemia and non-organ specific antibodies have not been extensively studied. Bloch *et al* (1965) compared the first degree relatives of nine patients with Sjögren's syndrome with nine control families. They found a significantly increased incidence of 'probable' rheumatoid arthritis, positive Schirmer's tests, hyperglobulinaemia, and raised thyroid antibody titres in those relatives under 45 in the group with Sjögren's syndrome. The authors suggested that this disorder might be due to an inherited immunological defect.

There have been many studies on the families of patients with renal tubular acidosis, but only one has used immunological techniques. Wilson *et al* (1967) studied the relatives of two patients with renal tubular acidosis. No further cases of renal tubular acidosis were detected. There was, however, a significant mean elevation of the IgG fraction in these relatives compared with the IgG mean in the control families. The authors suggested that renal tubular acidosis should be included in the group of autoimmune diseases.

Diffuse pulmonary fibrosis may occur in families, but only one study has used immunological techniques. Bonanni *et al* (1965) studied a family with eight proven and three suspected cases of pulmonary fibrosis. All four patients tested had gamma-globulin abnormalities which suggests that immunological mechanisms were involved in the pathogenesis of the lung lesion.

We have been unable to find any record of family studies performed on patients with purpura or peripheral neuropathy associated with hyperglobulinaemia.

Multiple immunological abnormalities have been recorded in the same family. Fudenberg, German and Kunkel (1962) reported a family in which the proband had agammaglobulinaemia. Other immunological disorders detected in this family were chronic discoid lupus erythematosus and rheumatoid arthritis. There was a high incidence of positive serological and gamma-globulin abnormalities in the asymptomatic relatives. Rotstein and Good (1962) also found a high incidence of immunological abnormalities in the family of a patient with agammaglobulinaemia.

The present study differs from previous reports in that a number of diseases associated with hyperglobulinaemia and non-organ specific antibodies have been specifically looked for in those relatives with an immunological abnormality. The results obtained suggest that there might be an inherited predisposition to develop immunological abnormalities. In the majority these abnormalities were present without the subject suffering from any disease, but in some, other factors, possibly environmental, may precipitate one or more of a number of associated clinical syndromes. It is thus of importance to investigate the relatives of patients with one of these disorders for the presence of immunological abnormalities and the other disorders associated with them.

We thank Dr J. Bamforth for permission to study the proband, and Dr G. Franglen and Mr R. Lloyd for performing the immunological investigations.

The work was supported by grants from the Medical Research Council (for A.M.S.M.) and the London Hospital free funds (for P.L.G.).

References

- Ball, J. (1950). Serum factor in rheumatoid arthritis agglutinating sensitised sheep red cells. *Lancet*, 2, 520-524.
- Bloch, K. J., Buchanan, W. W., Wohl, M. J., and Bunim, J. J. (1965). Sjögren's syndrome. A clinical pathological and serological study of 62 cases. *Medicine (Baltimore)*, 44, 187-231.
- Bonanni, P. P., Frymoyer, J. W., and Jacox, R. F. (1965). A family study of idiopathic pulmonary fibrosis. *Amer. J. Med.*, 39, 411-421.
- Coons, A. H., and Kaplan, M. H. (1950). Localization of antigen in tissue cells. II. Improvements in a method for the detection of antigen by means of fluorescent antibody. *J. exp. Med.*, 91, 1-30.
- Fudenberg, H. H., German, J. L., III, and Kunkel, H. G. (1962). The occurrence of rheumatoid factor and other abnormalities in families of patients with agammaglobulinemia. *Arthr. and Rheum.*, 5, 565-588.
- Fulthorpe, A. J., Roitt, I. M., Doniach, D., and Couchman, K. (1961). A stable sheep cell preparation for detecting thyroglobulin autoantibodies and its clinical applications. *J. clin. Path.*, 14, 654-660.

- Kaltreider, H. B., and Talal, N. (1969). The neuropathy of Sjögren's syndrome. *Ann. intern. Med.*, **70**, 751-761.
- Lawrence, J. S. (1965). Epidemiology and genetics of rheumatoid arthritis. In *Rheumatology—Annual Review*, edited by J. Rotstein, vol. 2, p. 29. Karger, Basle.
- Leonhardt, E. T. G. (1967). Family studies in systemic lupus erythematosus. *Clin. exp. Immunol.*, **2**, 743-759.
- Mason, A. M. S., and Golding, P. L. (1970a). Renal tubular acidosis and autoimmune thyroid disease. *Lancet*, **2**, 1104-1107.
- Mason, A. M. S., and Golding, P. L. (1970b). Hyperglobulinaemic renal tubular acidosis: a report of nine cases. *Brit. med. J.*, **3**, 143-146.

- Osler, A. G., Strauss, J. H., and Mayer, M. M. (1952). Diagnostic complement fixation; method. *Amer. J. Syph.*, **36**, 140-153.
- Rotstein, J., and Good, R. A. (1962). Significance of the simultaneous occurrence of connective tissue disease and agammaglobulinaemia. *Ann. rheum. Dis.*, **21**, 202-206.
- Wilson, I. D., Williams, R. C., and Tobian, L., Jr. (1967). Renal tubular acidosis. Three cases with immunoglobulin abnormalities in the patients and their kindreds. *Amer. J. Med.*, **43**, 356-370.
- Wrong, O., and Davies, H. E. F. (1959). The excretion of acid in renal disease. *Quart. J. Med.*, **28**, 259-313.

The October 1971 Issue

THE OCTOBER 1971 ISSUE CONTAINS THE FOLLOWING PAPERS

Lymphocytic tumours of the conjunctiva GWYN MORGAN

Recurrent hyperparathyroidism due to parathyroid carcinoma H. A. ELLIS, M. FLOYD, AND F. K. HERBERT

Histological findings in pseudomembranous trigonitis L. HENRY AND M. FOX

Pathology of Tangier disease PATRICIA M. BALE, P. CLIFTON-BLIGH, B. N. P. BENJAMIN, AND H. M. WHYTE

Histochemical detection of the enzyme deficiency in blood films in Wolman's disease BRIAN D. LAKE

Idiopathic thrombocytopenic purpura with normal platelet survival time G. W. K. DONALDSON, A. C. PARKER, M. MCARTHUR, AND J. RICHMOND

Identification of a congenital defect of factor VII in a colony of beagle dogs: the clinical use of the plasma L. POLLER, JEAN M. THOMSON, C. H. J. SEAR, AND WENDY THOMAS

Part I Identification of the clotting defect in a colony of beagles

Part II Clinical applications

Part III Quality control of tissue thromboplastin extracts by factor VII-deficient plasma

A method for studying antibiotic concentrations in inflammatory exudate J. A. RAEBURN

Colicine types of *Shigella sonnei* isolated in Hong Kong C. H. CHAN-TEOH, W. T. WONG, C. T. HUANG, AND H. SHUM

Identification of *Corynebacterium diphtheriae* by immunofluorescence during a diphtheria epidemic A. W. MCCracken AND C. U. MAUNEY

Copies are still available and may be obtained from the PUBLISHING MANAGER, BRITISH MEDICAL ASSOCIATION, TAVISTOCK SQUARE, WC1H 9JR price £1.05

Chick embryo inoculation as a pathogenicity test for *Candida* species BETTY M. PARTRIDGE, M. A. ATHAR, AND H. I. WINNER

Study on dioxan separation in the radioimmunoassay of human growth hormone, human chorionic gonadotrophin, adrenocorticotrophic hormone, and insulin M. STAHL, J. GIRARD, J. B. BAUMANN, AND P. W. NARS

Abbreviations for names of enzymes of diagnostic importance D. N. BARON, D. W. MOSS, P. G. WALKER, AND J. H. WILKINSON

Beta-propiolactone as an agent for enzyme sterilization K. J. STOKES

On-line acquisition of the output of a multi-channel analyzer (SMA 12/60) by means of an Elliott computer system N. W. CARTER AND P. D. GRIFFITHS

Technical methods

Quantitative estimation of protein by electro-immunodiffusion on Cellogel acetate membranes J. WATKINS, BRENDA ATKINS, AND E. J. HOLBOROW

A simple capillary tube method for the determination of the specific gravity of 25 and 50 μ l quantities of urine R. H. WATTS

Demonstration of basement membrane in renal biopsies by silver-methenamine on thin epoxy-resin sections R. C. GLADWIN

Estimation of 3-O-methyl-D-glucose in the presence of glucose K. N. FRAYN AND P. I. ADNITT

Present day practice

Pitfalls of Australia antigen detection and screening J. KOHN AND J. R. MORGAN

Letters to the Editor

Book reviews