

Multiple immunological abnormalities in a family

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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

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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

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.

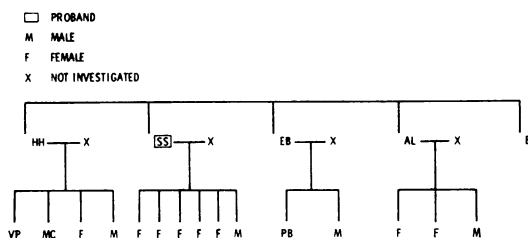


FIG. 1. THE FAMILY PEDIGREE

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
<i>Immunoglobulins</i>								
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
<i>Autoantibodies</i>								
Wassermann reaction	-	-	-	-	-	+	-	-
Coombs test	-	-	-	-	-	+	-	-
Rheumatoid screen	+	-	+	-	-	-	-	-
Sheep cell agglutination test	-	-	1/80	-	-	-	-	-
Antinuclear antibody	+++	++	-	-	-	-	-	++++
Smooth muscle antibody	-	-	++++	-	-	-	-	-
Mitochondrial a/b	-	-	-	-	-	-	-	-
<i>Autoimmune complement-fixation tests</i>								
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 a 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.

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