Severe selective IgM deficiency

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SYNOPSIS Among the primary antibody deficiency syndromes, severe selective IgM deficiency (also previously known as type V dysgammaglobulinaemia) is rare, and the majority of previous reports have indicated a fatal outcome.

Three adult patients who were found to have a persistently low serum IgM are described. This deficiency was not obviously related to their presenting illness; in two of the patients, who were investigated in detail, it appeared to be of no immediate consequence.

Selective IgM deficiency is not an uncommon finding. In a retrospective study of 3000 patients at this hospital, excluding those with conditions such as myelomatosis, leukaemia, and lymphoma, an incidence of 3% was found, and others have reported incidences of 1% (Hobbs *et al*, 1967a) and 3.8% (Kelly *et al*, 1970).

Selective IgM deficiency is recognized as occurring in association with coeliac disease (Asquith *et al*, 1969) and other protein-losing enteropathies, acute and chronic meningococcal septicaemia (Hobbs *et al*, 1967a; Fass and Saslaw, 1972; Jones *et al*, 1973), in atopic individuals (Kaufman and Hobbs, 1970), and as a familial condition (Hobbs *et al*, 1967a; Jones *et al*, 1973). Serum IgM levels may be selectively depressed in the Wiskott-Aldrich syndrome and in the Giedion Scheidegger syndrome (Giedion and Scheidegger, 1957), and low levels have also been reported, as part of a complex immunological defect, in a family who suffered recurrent viral infections (Silver *et al*, 1973).

However, a severe selective IgM deficiency, as arbitrarily defined by serum levels of 10% or less of the normal mean for age and sex (Kaufman and Hobbs, 1970), has been reported infrequently; a summary of cases previously reported in detail is given in table I (Hobbs *et al*, 1967a; Stoelinga *et al*, 1969; Faulk *et al*, 1971). The three patients described in this report were not suffering from any of the above conditions, and two showed no tendency to infection; yet they showed very low IgM levels on repeated estimations.

Immunological methods

Serum IgG, IgA, and IgM were measured by the
Received for publication 28 January 1976

single radial diffusion technique (Fahey and McKelvey, 1965) using a serum of known immunoglobulin concentration as standard. Immunoglobulins and secretory component in jejunal fluid were detected in a semiquantitative double diffusion Ouchterlony test in agarose using specific antisera.

Escherichia coli antibodies were detected by passive haemagglutination (Webster *et al*, 1974), and lymphocyte transformation to mitogens and antigens was performed on whole blood by the method of Paty and Hughes (1972) using defibrinated blood and culturing the cells in Roswell Park Medium (RPMI) with 10% normal homologous AB serum. Mitogens added to the cultures were phytohaemagglutinin (PHA) at concentrations of 2.0 µg/ml and 0.2 µg/ml, and Pokeweed mitogen (PWM). Antigens added were purified protein derivative (PPD), *Candida albicans*, and tetanus toxoid. The PHA cultures were terminated at three days and the other mitogen and antigen cultures at seven days. T-cell 'E' rosettes and B-cell 'EAC' rosettes in the peripheral blood were estimated by the methods of Stjernswärd *et al* (1972), lymphocytes being separated from defibrinated blood on a Ficoll/Triosil gradient. Lymphocytes containing immunoglobulin markers on their surface were detected by the method of Papamichail *et al* (1971), using anti-Fab, -gamma, -alpha, and -mu chain conjugates.

Case histories

CASE 1

A 65-year-old Yemeni man presented with bloody diarrhoea of six months' duration. He had previously been diagnosed as suffering from diabetes mellitus controlled with diet and tolbutamide. Sigmoido-

Author	Age	Sex	Presentation	IgM level ¹	Other immunological abnormalities	Outcome
Hobbs <i>et al</i> (1967a)	8 yr	M	Acute meningococcal septicaemia	3.6%	Father, paternal uncle, first cousin had low IgM	Death
	5 yr	M	Acute meningococcal septicaemia	10.9%	Father had low IgM	Death
Faulk <i>et al</i> (1971)	8½ mth	M	<i>Pseudomonas</i> nasopharyngitis	Undetectable	Father had low IgM. Eosinophilia, neutropenic leucopaenia, and spleen and lymph nodes lacked germinal centres	Death
Stoelinga <i>et al</i> (1969)	13 yr	M	Recurrent infections	6.4%	Father had low IgM. Severe recurrent pneumonia, autoimmune haemolytic anaemia, and chronic eczema	Recovery after infection

Table 1 Cases with severe IgM deficiency reported in detail

Expressed as a percentage of the normal mean for age and sex

scopy showed a granular mucosa with contact bleeding, and a rectal biopsy was compatible with non-specific ulcerative colitis. A barium enema showed that this was confined to the rectum and sigmoid colon.

Investigations were as follows: ESR 4 mm/hour. Haemoglobin 13.2 g/dl. Platelets, red cell folate, and vitamin B₁₂ normal. A bone marrow aspiration showed a micronormoblastic picture with depletion of iron stores; plasma cells and lymphocytes were within normal limits. A chest x-ray showed evidence of old healed tuberculosis.

Tests of intestinal function: xylose absorption, as measured by a one-hour blood level, serum orosomucoids, and urinary indicans were all normal. There was no steatorrhoea and no infective or parasitic agent was isolated from the faeces.

A peroral jejunal biopsy showed grade I changes (Roy-Choudhury *et al*, 1966) with normal disaccharidase levels. On immunofluorescence, numerous IgM plasma cells were seen, but there was no free IgM in the tissue spaces. In addition, no IgG plasma cells were seen, but both IgA plasma cells and free IgA were present. In the jejunal aspirate IgM was not detected, and lipase and protease levels were normal. The rectal biopsy on immunofluorescence showed IgM, IgG, and IgA plasma cells. Liver function (as measured by total protein, albumin, transaminases, alkaline phosphatase, and total bilirubin) was normal, and the patient was negative for hepatitis B antigen (HB Ag).

The patient was treated with systemic steroids followed by a remission of the proctosigmoiditis. He was followed for a period of seven months and during this time he did not develop any evidence of disease in the reticuloendothelial system and serum IgM values were unaltered by steroid treatment. He subsequently returned to the Yemen and was not followed up.

CASE 2

A 72-year-old English man presented with diarrhoea of three months' duration. He had suffered from ischaemic heart disease and had been treated with digoxin, 0.25 mg three times a day, for chronic congestive cardiac failure. His only other previous illness had been intermittent claudication treated with a Teflon graft in the right femoral artery, and, because of this, he was taking warfarin.

Examination, including sigmoidoscopy, was normal apart from a smoothly enlarged liver 10 cm below the costal margin. There was no splenomegaly. Investigations were as follows: ESR 6 mm/hour. Haemoglobin 12.4 g/dl. Platelets, red cell folate, and vitamin B₁₂ normal. Bone marrow aspiration showed normoblastic erythropoiesis and normal numbers of plasma cells and lymphocytes. A chest x-ray was normal.

Tests of intestinal function were carried out identically with those of case 1 and were normal. A peroral jejunal biopsy showed a normal mucosa and disaccharidases. On immunofluorescence IgM plasma cells were not seen. However, IgA and IgG plasma cells were present together with numerous eosinophils. In the jejunal aspirate IgM was not detected, and lipase and protease levels were normal. Liver function, measured as in case 1, was normal and HB Ag was negative. The urea was slightly raised at 11.6 mmol/l but there was no other evidence of renal disease. A barium enema showed diverticulosis.

Digoxin was discontinued and restarted at a lower dose, followed by rapid remission of the diarrhoea. He was known to be alive and well five months after the IgM had been found to be low.

CASE 3

A 60-year-old Polish man was admitted with dyspnoea and a productive cough of two months' duration. A chest x-ray showed bilateral shadowing

suggestive of tuberculosis; this was confirmed with a positive culture for acid alcohol fast bacilli from a laryngeal swab. Investigations were as follows: ESR 56 mm/hour. Haemoglobin 12.5 g/dl. Platelets normal. Liver function measured as in case 1 was normal. HB Ag was negative.

He died 12 days after admission before his immunological status could be fully assessed.

A necropsy confirmed tuberculous broncho-

pneumonia. The reticulo-endothelial system was normal, as were all other systems.

Results

The immunological findings are summarized in tables II and III. The normal values given are expressed as a mean $\pm$ 2 SD except those for lymphocyte transformation in which the values were

Investigations	Case 1	Case 2	Case 3
Serum IgM values ¹ (0.21–1.40) ²	0.05, 0.04, 0.06 0.07, 0.06, 0.00 0.03, 0.02, 0.00	0.15, 0.11 0.06 0.06	0.04 0.04
Mean serum IgM ¹	0.037	0.107	0.040
Percentage of normal mean	4.6	13.3	5.0
Mean serum IgG ¹ (6.00–16.00) ²	9.97	7.03	9.83
Mean serum IgA ¹ (0.90–5.20) ²	2.49	4.03	5.51
Blood group	B Rh neg	A Rh pos	—
Isohaemagglutinins	No anti A	Very weak anti B	Anti A and B present
<i>E. coli</i> antibodies (> 1:32)	1:4	1:8	Nil
Widal (before inoculation)	Negative	Negative	—
(after inoculation)	Positive H and O Ab	—	—
Bone marrow (fluorescent microscopy)	—	IgM cells present	—
Jejunal biopsy	Normal numbers of IgM plasma cells present	No IgM plasma cells present	—
Jejunal aspirate	IgM nil: IgA, IgG present	IgM nil: IgA, IgG present	—
Secretory component	Present	Present	—

Table II Immunological findings in serum, bone marrow, jejunal tissue, and jejunal aspirate

¹Expressed as g/l

²Normal ranges in brackets mean $\pm$ 2 SD

³Normal ranges in brackets calculated as a lognormal distribution

—Test not done

Investigation	Case 1	Case 2	Case 3
Mean absolute lymphocyte count (1500–3500) ¹	914	2190	760
Percentage of total WBC (20–50%)	12.5	24	19
Cutaneous reaction to antigen at 48 hours:			
PPD 1 in 1000 (Evans Medical)	Positive	Negative	Negative
<i>Candida albicans</i> (Bencard)	Negative	Negative	—
Trichophyton (Bencard)	Negative	Negative	—
Lymphocyte transformation:			
ratio of test to control:			
Mitogen ²			
PHA 2.0 μ g (93–918)	74	175	—
PHA 0.2 μ g (30–700)	24	88	—
PWM (11–255)	4.2	60	—
Antigen ²			
PPD (14–225)	0.8	28	—
<i>Candida albicans</i> (1.3–10.9)	0.7	1.3	—
Tetanus toxoid (0.9–8.2)	0.8	1.0	—
T and B cell rosettes ¹			
T cells (35–57%)	49	18	—
B cells (22–42%)	35	46	—
Surface immunofluorescence ¹ (23–43%)	24	48	—

Table III Lymphocyte count, lymphocyte transformation, and T and B cell quantitation

¹Normal ranges in brackets mean $\pm$ 2 SD

²Normal ranges in brackets calculated as a lognormal distribution

—Test not done

converted to logarithms to produce a more normal distribution and the means ± 2 SD were then calculated.

The values of zero IgM for case 1 indicate undetectable levels. This patient showed evidence of a defect of both humoral and cellular immune systems with a diminished lymphocyte transformation response to both PHA and PWM and to the three antigens with which his lymphocytes were cultured. However, the distribution of T and B cells in the peripheral blood was within the normal range. He had no detectable isoagglutinins and a very low *E. coli* antibody titre, both tests being indicative of IgM antibodies. Nevertheless he was able to produce IgM antibodies (giving positive anti 'O' antibodies) in response to TAB vaccination although the serum level of IgM remained unchanged. He had normal numbers of IgM plasma cells in the jejunal and rectal mucosae and he had a normal number of IgM staining B lymphocytes in the peripheral blood.

Case 2 showed primarily an abnormality of the humoral system, though delayed hypersensitivity skin tests were negative and he had a reduced number of T cells in the peripheral blood which, however, responded normally to mitogen and antigen stimulation. The increased number of B cells were accounted for by a preponderance of IgM (approximately 50% of the cells staining for surface immunoglobulin) despite the low serum level of this immunoglobulin.

Case 3 had a negative skin test to PPD in the presence of active tuberculosis. Although he had no detectable *E. coli* antibodies, he was able to produce isoagglutinins.

Discussion

In the three patients presented here, neither the causes nor the consequences of their low IgM was apparent.

IgM is found in all vertebrates; in some of the more primitive, such as the shark, it is the only immunoglobulin present. IgM is the first immunoglobulin detectable in the human fetus, being found as early as 10.5 weeks' gestation in the developing embryonic spleen and 35 weeks' gestation in the serum (Gitlin and Biasucci, 1969). It is thought to have a role in defence against bloodborne bacterial infections, and viral neutralizing antibodies are often of the IgM type. Experimentally, IgM antibodies are the first to be produced on initial exposure to an antigen.

The synthetic rate of IgM is 3.3 mg/kg per day with a half-life of 10 days; the fractional catabolic rate (FCR) is 8.8% per day (Rothschild and Waldmann, 1970); the synthetic rate and FCR are

independent of serum levels. The FCR may be accelerated in conditions associated with a protein losing enteropathy, and reduction in synthesis may occur in agammaglobulinaemia, myelomatosis, and coeliac disease. Approximately 80% of IgM is intravascular (Cohen and Freeman, 1960) and so it is theoretically possible that haemoconcentration or dilution might affect the serum level.

IgM levels may vary between races (Hardy *et al*, 1969); the raised serum level observed in West African communities compared to healthy British adults (Rowe *et al*, 1968) has been attributed to increased antigenic load due to parasitic infections. In all populations a higher IgM level is found in females compared to males. Although this is more marked in the reproductive years, there is still a difference after the menopause.

It seems likely that the cases presented here have deficient synthesis of IgM, although in one (case 1), normal numbers of IgM plasma cells were seen. In addition to their common humoral defect, cases 1 and 2 both showed differing impairment of cell-mediated immunity.

In case 3 there is a possibility of an immune defect associated with tuberculosis, although this type of immunological defect has not previously been reported. Whether the defect of IgM production is inherited or acquired may only be speculated and familial studies could not be done.

In males with sex-linked hypogammaglobulinaemia a marked reduction in infections may be observed after replacement therapy with IgG immunoglobulin, without raising the level of IgA or IgM, and it seems possible to keep free of systemic bacterial and other infections despite a very low level of IgM, presumably because enough protective IgG antibodies exist. Possibly IgM is less important as a protective antibody in late adulthood, since infections at that age are likely to represent a secondary antigenic challenge and produce a brisk IgG response.

These cases illustrate the complexity of the physiological role of IgM.

We thank Professor Morgan, Dr Geddes, and Dr Springett for permission to study their patients.

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