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Hypocomplementaemia due to a genetic deficiency of β1H globulin

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SUMMARY

An 8-month-old Asian boy who presented with the haemolytic uraemic syndrome was found to have a low haemolytic complement, and in particular a very low C3 level, with a normal C4 level. These abnormalities persisted after recovery and were not associated with the presence of circulating C3 nephritic factor. A clinically healthy 3-year-old brother was found to have an identical complement profile, which indicated increased alternative pathway activation. Both brothers had normal levels of the C3b inactivator, but very low levels of β1H globulin (less than 10% of a reference standard serum). The parents, who were first cousins, had half-normal levels of β1H globulin, and low levels were found in other members of the family, indicating that the defect was inherited.

INTRODUCTION

Beta-1H globulin is a plasma protein first described by Nilsson & Müller-Eberhard (1965) as a contaminant in preparations of C5. Its function was discovered more than 10 years later when it was shown by Whaley & Ruddy (1977) to be identical with the co-factor which accelerated the inactivation of C3b by the C3b inactivator (Whaley & Ruddy, 1976). Hence, it acts together with the C3b inactivator as a modulator of the activation of the alternative pathway of complement. *In vitro* depletion of serum β1H (Whaley & Thompson, 1978) by a specific antiserum has been shown to cause complete C3 consumption by activation of the alternative pathway, an effect similar to that achieved by depletion of the C3b inactivator itself (Nicol & Lachmann, 1973).

Patients with a complete deficiency of the C3b inactivator have been described (Alper *et al.*, 1970; Thompson & Lachmann, 1977). These patients presented with recurrent bacterial infections and were found to have low C3 levels due to exhaustive alternative pathway activation with virtually absent factor B levels and absence of 'total' alternative pathway activity. Their fresh plasmas were shown to contain appreciable amounts of circulating C3b (approximately 40–50% of the immunochemical C3), but were negative for free C3d. The C3 level was about 30% of normal but C3 synthesis was anomalously high for this low serum level, in being approximately normal. Other patients with low serum levels associated with excessive C3 consumption show a reduction in synthesis (Charlesworth *et al.*, 1974), presumably due to feedback inhibition by circulating free C3d. The red cells of the C3b-inactivator-deficient patients were Coombs-positive for C3, reacting with both anti-C3c and anti-C3d antisera. Nicol & Lachmann (1973) showed that *in vitro* depletion

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of the C3b inactivator in the presence of autologous red cells resulted in the cells becoming coated with C3b as a 'bystander' effect of excessive C3 activation.

This paper reports a family in which two members were found to have very low C3 levels with evidence of alternative pathway activation. The propositus is the fourth child of Asian parents born in the UK.

CASE HISTORY (W.)

After a full-term normal delivery the child gained weight on the 75th centile and was well until the age of 8 months when he was admitted to East Birmingham Hospital with increasing pallor for 2 days and vomiting for 5 days. His parents, who were first cousins, and four siblings were in good health and there was no family history of renal disease or recurrent infections. On admission he was not dehydrated but was markedly anaemic with a haemoglobin of 5 g/dl. His blood film showed numerous schistocytes and burr cells, 14% reticulocytes and his platelet count was slightly reduced to 80×10^9/l. His urine showed 3+ protein, numerous red blood cells and granular casts and 2 days after admission his serum urea and creatinine were found to be elevated at 42 mmol/l and 135 μmol/l respectively (normal for age: urea 3–7 mmol/l; creatinine 25–45 μmol/l). His serum fibrin degradation products (10–40 μg/ml) and thrombin clotting time (20 sec, control 15 sec) were slightly elevated and a diagnosis of haemolytic uraemic syndrome was made. No pathogenic bacteria were isolated from his nose, throat or stool but advenovirus type 2 was subsequently grown from his stool.

His serum C3 was found to be very low (0·18 g/l; normal 0·75–1·75) and his C4 was within the normal range. His red cells gave a positive antiglobulin test for C3d but were negative for antibody. A renal biopsy was obtained 15 days after admission and examined by light and electron microscopy (Dr C. W. Edwards). In 46 glomeruli there was diffuse mesangial and endothelial cell proliferation and swelling with capillary wall thickening due to subendothelial deposits of floccular material which was also seen in the mesangium. A few capillary loops contained hyaline thrombi but the large vessels were normal. The interstitium was normal and the tubules showed only minor vacuolation with a few casts. No glomeruli were identified in the material for immunofluorescence studies but the histological appearances were characteristic of haemolytic uraemic syndrome (Kaplan, Thomson & de Chaderevian, 1976).

He was treated by maintenance of his fluid balance, protein and sodium restriction and a single transfusion of washed, packed red cells. His vomiting stopped after 6 days and he was never oliguric. His blood urea fell to normal after 12 days but he experienced a setback 3 weeks after admission when he developed bilateral otitis media due to *Haemophilus influenzae*. There was a sharp fall in his haemoglobin from 8·4 to 5·6 g/dl and a rise in his blood urea to 13·5 mmol/l but the number of reticulocytes, fragmented red cells and platelets did not change. There was a good response to treatment with ampicillin and he was discharged after 2 weeks with a haemoglobin of 10·8 g/dl, urea 9·5 mmol/l, creatinine 40 μmol/l and no proteinuria.

Four weeks later he was readmitted with fever and vomiting due to left otitis media. His haemoglobin had fallen to 7·8 g/dl and his serum urea and creatinine had risen to 13·4 mmol/l and 85 μmol/l respectively. Fragmented red cells were again seen in his blood film, the direct antiglobulin test for C3d on the red cells was again positive and his urine contained 3+ protein but his platelet count (305×10^9/l) was normal. His blood pressure was raised (150/110 mm Hg) having consistently been normal beforehand. The hypertension responded to treatment with bendrofluazide and oxprenolol and the fever to treatment with antibiotics. Over the next 2 months it was possible to stop hypotensive therapy and when seen in the clinic 7 months after his initial admission he was well, blood pressure 90/60, haemoglobin 12·2 g/dl, reticulocytes $< 2\%$, serum creatinine 30 μmol/l and his urine contained no protein and only 10 RBC/mm^3.

Throughout the course of his illness, both during exacerbations and during intervening periods of good health, his serum C3 remained very low with a normal C4 and his serum was negative for C3 nephritic factor activity. Accordingly, a more detailed study of the complement system of the patient and his family was undertaken.

MATERIALS AND METHODS

Specimens. Blood was taken into EDTA for analysis of the plasma and red cells, and into plain glass tubes for the collection of serum. Serum was obtained by centrifugation after the tubes had stood at room temperature for 1 hr. The plasma was obtained by centrifugation of the EDTA specimen within 20 min, and the red cells were washed three times in veronal-buffered saline before being tested for agglutination by specific antisera. Heparinized blood was also sent for tissue typing.

Complement. Functional CH50 haemolytic levels were measured according to the method of Mayer (1961) using sheep erythrocytes (E) coated with the IgM fraction of rabbit antibody (A).

C'142' test was performed by a modification of the method previously published (Thompson, 1972). Briefly, aliquots of EA were added to dilutions of serum for 8–10 min at 32°C, then excess of guinea-pig (Gp) serum in 0·04 M EDTA was added, and incubation continued at 37°C for 30 min. The result was expressed as the titre of serum producing greater than 50% lysis.

Immune adherence was performed according to the method of Lachmann, Hobart & Aston (1973) and expressed as the highest titre of serum which produced a settling pattern of a 1% mixture of human Gp O red cells and EA. C4 was measured by adding dilutions of test serum to a mixture of EA in C4-deficient guinea-pig serum (Gwynn & Thompson, 1978). C2 was measured using EAC1, 4 cells and guinea-pig serum in EDTA (Thompson, 1978). Total alternative pathway activity was measured using rabbit erythrocytes suspended in Mg EGTA (Platts-Mills & Ishizaka, 1973) and by the lysis of guinea-pig E in Mg EGTA suspended in agarose plates (Lachmann *et al.*, 1973). C7 was measured by the reactive lysis procedure (Thompson & Lachmann, 1970).

Immunochemical quantitation of C1q, C4, C2, C3, C5, C8, factor B, factor P, C1 esterase inhibitor, C3b inactivator and β1H globulin were carried out by the single radial diffusion technique using monospecific antisera. Two anti-β1H globulin antisera were used, a goat anti-β1H kindly donated by Dr K. Whaley, and a commercial sheep anti-β1H (Seward Laboratories).

C1r, C1s, C6, C9 and C4 binding protein were assessed by semiquantitative double-diffusion analysis in agarose gel using monospecific antisera.

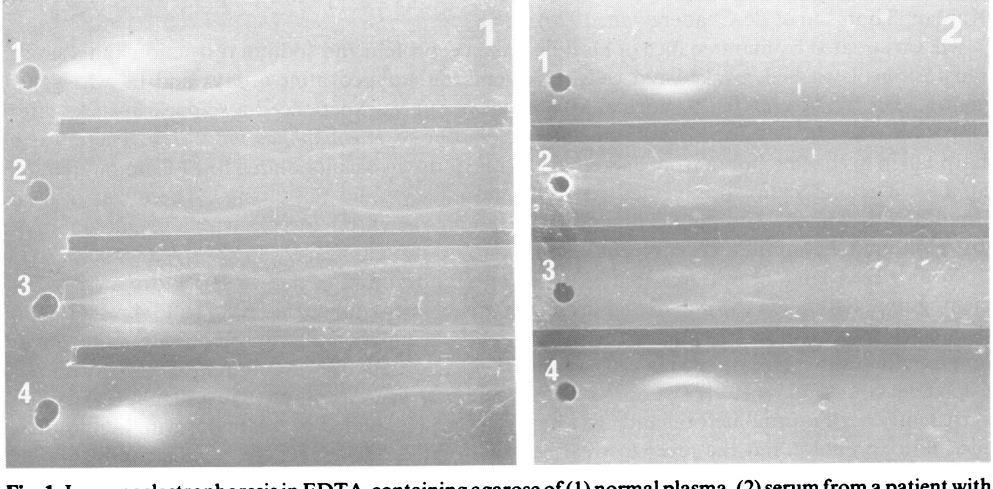

Fig. 1. Immunoelectrophoresis in EDTA-containing agarose of (1) normal plasma, (2) serum from a patient with hypocomplementaemic mesangioproliferative glomerulonephritis, (3) plasma from patient W., and (4) plasma from patient's brother (Z.). After electrophoresis, troughs were filled with antiserum to C3d (anti-α2D). Anode was to the right.

Fig. 2. Immunoelectrophoresis in EDTA-containing agarose of (1) normal plasma, (2) plasma from patient W., (3) plasma from patient's brother (Z.), and (4) plasma from patient's mother. Anti-factor B antiserum was placed in the troughs. The anode was to the right.

Complement breakdown products were assessed by immunoelectrophoresis in fresh EDTA plasma using anti-C3c, anti-C3d and anti-factor B antisera. Anti-C3d (α2D) was obtained from the Netherlands Red Cross Blood Transfusion Service. Agglutination of thrice-washed red blood cells from the patient and his relatives was tested against antisera specific for C3c, C3d, C4, IgG and β1H globulin. C3 nephritic factor was tested by incubating 1 vol of test serum with 2 vol of normal serum for 45 min at 37°C, and determining the extent of C3 conversion by immunoelectrophoresis. Results were scored as positive (+ to +++) or negative. Tissue typing was done by the method of Terasaki (Mackintosh, 1977).

RESULTS

Patient W. and his 3-year-old clinically healthy brother, Z., were found to have an identical complement profile. Their washed red cells, from blood taken into EDTA, were strongly positive for C3d, but negative for C3c, C4, IgG and β1H globulin.

Table 1. Complement levels in the propositus (W.) and his brother (Z.)

	W.	Z.	Normal range
Classical pathway components			
Functional			
CH50 (u/ml)	13	11	25–45
C'142' (titre)	800	400	800–1,600
Immune adherence (titre)	640	640	640–2,560
C4 (u/ml)	80,000	65,000	30,000–100,000
C2 (u/ml)	1,250	1,400	1,200–3,000
C1 inhibitor (% standard)	120	85	75–140
Immunochemical			
C1q (% standard)	40	70	60–120
C4 (g/l)	0·37	0·32	0·14–0·54
C2 (% standard)	88	75	70–150
C3 (g/l)	0·12	0·17	0·75–1·75
C1 inhibitor (g/l)	0·40	0·24	0·18–0·26
Alternative pathway components			
Functional			
Total activity			
Rbt E (u/ml)	4·5	6·0	12–26
Gp E in agarose (% standard)	20	25	—
Immunochemical (% standard)			
Factor B	35	32	70–150
Factor P	60	60	60–130
Factor I (C3b INA)	90	100	80–130
Factor H (β1H)	6	7	70–140
'Attack' mechanism components			
Immunochemical			
C5 (% standard)	100	82	70–120
C7 (% standard)	150	130	70–140
C8 (% standard)	110	110	80–140

C1r, C1s, C6, C9 and C4 binding protein were present in normal amounts on semiquantitative double-diffusion analysis using monospecific antisera.

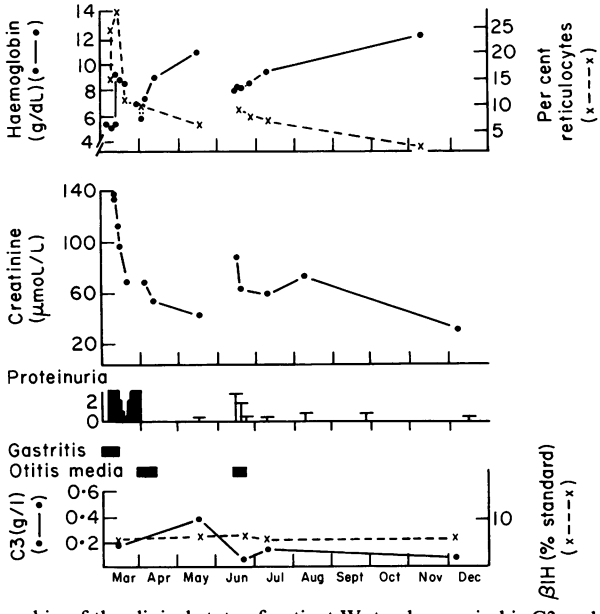

Fig. 3. Relationship of the clinical state of patient W. to changes in his C3 and β1H levels.

Immunoelectrophoresis of fresh EDTA plasma showed a small amount of native C3 with considerable quantities of free C3d as α2d (Fig. 1). Factor B was present in reduced amounts, but in the normal beta position (Fig. 2). Free C3b was not present in significant amounts.

The results of the measurement of functional and immunochemical parameters of complement and of individual components are given in Table 1. It can be seen that the main defects were in C3, in total alternative pathway activity and in alternative pathway components. The classical pathway components and their inhibitors were normal.

The C3b inhibitor was also normal, but β1H globulin was grossly decreased to less than 10% of the standard in each child. Serial studies (in retrospect on stored samples) of the patient's serum

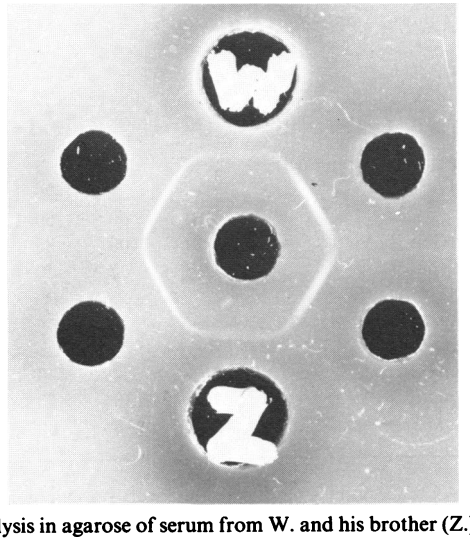

Fig. 4. Double-diffusion analysis in agarose of serum from W. and his brother (Z.). Anti-β1H antiserum was in the central well and normal sera in the unmarked outer wells.

Table 2. Complement levels in the family of patient W.

	CH50 (u/ml)	C3 (g/l)	Free C3d in plasma	C4 (g/l)	C2 (% standard)	Factor B (% standard)	Factor P (% standard)	C3b inact. (% standard)	β1H (% standard)
Generation 1									
Grandmother	48	0·95	+	0·45	n.d.	95	100	160	60
Generation 2									
Mother	34	0·75	+	0·38	100	90	85	100	55
Father	38	0·80	+	0·32	95	75	60	110	45
Father's brother 1	44	1·35	−	0·60	150	105	125	120	105
Brother 2	36	1·15	±	0·55	105	60	70	110	47
Sister	28	0·85	±	0·35	135	65	60	130	52
Generation 3									
Sister	32	1·40	−	0·40	135	105	140	130	100
Brother 1 (Z.)	13	0·17	+++	0·32	110	35	60	90	7
Brother 2	24	1·12	n.d.	>0·28	140	>70	70	110	65
Propositus (W.)	11	0·12	+++	0·37	88	32	60	100	6
Normal range	25–45	0·75–1·75	−	0·14–0·54	70–130	70–150	60–130	80–130	70–140

n.d. = Not determined.

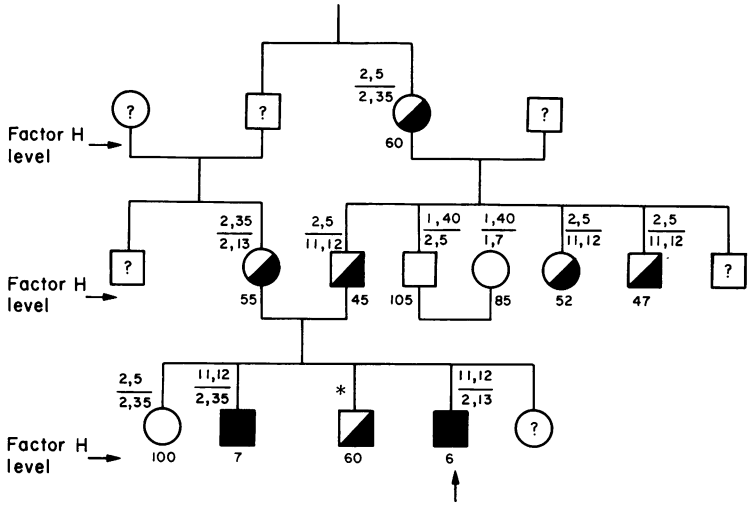

Fig. 5. Family tree of patient W. (*arrowed*) showing HLA haplotypes and β1H levels. (*) HLA type not available, (?) blood not available.

since the beginning of his illness showed the same low levels on four occasions over the 6-month period, with values of from 5 to 7% of the standard. The results of C3 and β1H globulin in relation to the patient's clinical state, haemoglobin and serum urea levels are shown in Fig. 3. Tests for C3 nephritic factor were negative.

The residual β1H globulin that was present in the sera of both brothers gave a reaction of identity with normal β1H (Fig. 4).

Family studies

Beta-1H globulin was also reduced in other members of the patient's family, but to a less marked degree. Otherwise, complement levels were within normal limits (Table 2). The parents of the patient were first cousins and had half-normal levels of β1H as had other members of the father's family and the paternal grandmother. From a study of HLA typing, the defect was not associated with HLA antigens (Fig. 5).

DISCUSSION

The low haemolytic complement levels in the serum of the patient and his clinically normal brother are clearly due to low C3 levels. There is evidence of alternative pathway activation with low factor B and reduced factor P levels, whereas the classical pathway components are normal.

The control proteins of the alternative pathway, β1H globulin and the C3b inactivator, are both required to modulate the action of this pathway. Clinical and experimental evidence has shown that a lack of the C3b inactivator causes complete activation of this pathway (Nicol & Lachmann, 1973), as does experimental depletion of β1H globulin (Whaley & Thompson, 1978). The evidence of the complement pattern in this family suggests that the C3 activation via the alternative pathway in the patient and his brother is the consequence of very low β1H globulin levels, and that this is the result of a genetic defect present in a great-grandparent and transmitted in the homozygous state to the affected children because of the consanguinity of their parents.

However, β1H globulin is consumed in the process of C3b inactivation and the possibility exists of another mechanism causing increased C3 breakdown via alternative pathway activation, with low β1H globulin levels as a consequence of this. C3 nephritic factor causes very low C3 levels due to alternative pathway activation. However, the plasma concentration and metabolic turnover of β1H

are normal in the presence of C3Nef (Charlesworth *et al.*, 1979) since it prevents the binding of β1H globulin to C3b and stabilizes the alternative pathway convertase. Moreover, C3 nephritic factor was not detected in the patient's serum even at the height of his illness. β1H globulin levels have been studied in other diseases in which complement consumption occurs, and although low levels have been reported, the lowest has been of the order of 30–40% of the mean normal (Whaley, Widener & Ruddy, 1978).

The most convincing evidence for an inherited defect of β1H globulin in this patient comes from the family study which shows classical Mendelian inheritance of the defective gene. The parents have half-normal β1H levels and are heterozygotes for the abnormal gene. A question arises as to the nature of the gene defect, since both the patient and his homozygous deficient brother have some residual β1H globulin. If the defect is of a structural gene then it is one which does not involve a major antigenic determinant, since the residual protein is antigenically identical with normal β1H. A structural gene defect which resulted in increased catabolism of the protein is a possibility, or alternatively a regulator gene defect is also possible. Whatever the nature of the defect it is clearly not associated with the MHC products. If genetic polymorphism exists in β1H as in many other complement proteins, a study of the polymorphism in this family may throw more light on the situation.

The residual β1H globulin is functionally normal, since although increased C3 activation is occurring, there is considerable free C3d, both in the plasma and on the red cells indicating some β1H activity in association with the normal C3b inactivator. *In vitro* experiments showed complete C3 and factor B conversion on complete depletion of β1H globulin (Whaley & Thompson, 1978) so that the finding of appreciable residual factor B and free C3d suggests that the residual β1H is functional. Dr Keith Whaley has recently kindly confirmed functional activity of the residual β1H globulin in the sera of the propositus and his brother.

The features of the complement profile in this case resemble those described in patients with a genetic C3b inhibitor deficiency as shown in Table 3. The main difference is that this patient and his brother do not have a complete absence of the control protein, otherwise the similarities between the

Table 3. Comparison of C3b INA and β1H deficiencies

	C3b INA	β1H
Clinical	Recurrent infections	(i) Haemolytic uraemic syndrome (ii) Healthy
Severity of defect	Complete	5–10% present
Red blood cells	C3c +++ C3d +++	C3d +++
Plasma immuno-electrophoresis of C3	C3, C3b	C3, C3d
Plasma immuno-electrophoresis of factor B	Bb only	Native factor B
C3 level	30% normal	15% normal
Factor B level	0–10% normal	35%
Factor P level	15% normal	60% normal
Total alternative pathway function	0	30% normal
CH50	30% normal	25% normal

two types of defect might have been greater. The very low C3 levels in this case are probably due to feedback inhibition of C3 synthesis brought about by free C3d, and this in turn has contributed to the sparing of factor B, and the maintenance of residual alternative pathway activation.

Of interest is the relation of the defect to the clinical presentation in this case. Low serum C3 is commonly observed in the acute phase of the haemolytic uraemic syndrome, possibly as a result of alternative pathway activation by damaged red cells. However, the abnormality is usually transient whereas in this case the progress of the haemolysis and uraemia were unrelated to the persistently low levels of C3 and β1H globulin (Fig. 3). The cause of the syndrome is probably multifactorial and it seems doubtful that the inherited complement defect in our patient was causal. Recurrences of the haemolytic uraemic syndrome are extremely rare (Drukker *et al.*, 1975) and in our patient the recurrences may have been related to an increased susceptibility to haemolysis of the C3d-coated red cells.

In the cases of complete C3b inactivator deficiency, the exhaustion of the positive feedback C3b activation loop led to defective bacterial opsonization with consequent recurrent infections. Whether the patient or his brother will be at risk in the future from haemolytic uraemic syndrome or recurrent infections remains to be seen. Patients with chronically low complement have poor primary antibody responses to thymus-dependent antigens (Ochs *et al.*, 1979; Jackson, Ochs & Wedgwood, 1979). Some patients with low C3 levels secondary to nephritic factor do have recurrent infections (Alper, Block & Rosen, 1973), and low C3 has been implicated in the causation of chronic renal disease (Pussell *et al.*, 1980). Thus follow-up of this family should give a further insight into the function of the complement system and the biological importance of its control proteins.

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