Archives of Disease in Childhood, 1980, **55**, 471-473

Homozygous deficiency of the second component of complement presenting with recurrent bacterial meningitis

Y H THONG, DONALD A SIMPSON, AND HANS J MÜLLER-EBERHARD

Department of Paediatrics, and Department of Neurosurgery, Adelaide Children's Hospital, South Australia, and Department of Molecular Immunology, Scripps Clinic and Research Foundation, La Jolla, California, USA

SUMMARY A girl presented with purulent meningitis at ages 6, 8, and 11 years. She was in good health between these three episodes. When aged 16 one of her brothers also experienced an attack of pneumococcal meningitis. Complement studies showed lack of C2 in the patient and the brother, and intermediate values in the mother and a sister. No other member of the family was available for study.

The complement system consists of a number of serum proteins interacting in an orderly, sequential manner, somewhat analogous to the cascade mechanism of blood coagulation.[1] It is one of the principal mediators of the inflammatory response. As such, its biological roles include host resistance to infection and pathogenesis of inflammatory diseases.

Hereditary deficiency of the second component of complement (C2) is rarely encountered.[2] It is transmitted in autosomal codominant fashion. Although heterozygous individuals may remain asymptomatic, an increased susceptibility to collagen-vascular disorders has been reported. These patients are generally not predisposed to infective complications. In this report, we describe a patient with the unusual presentation of recurrent bacterial meningitis.

Case report

The patient is a white Australian girl, now 13 years old. She was born of a normal term delivery, and tolerated immunisations and childhood illnesses well. There was no undue susceptibility to infections and no record of head injury. She had been well until $6\frac{1}{2}$ years when she developed purulent meningitis. The cerebrospinal fluid (CSF) grew *Haemophilus influenzae* type b. Two years later she was again admitted with meningitis due to *Streptococcus pneumoniae* type 18. After this serious infection, she was left with intellectual impairment and a slight left hemiparesis. At age $11\frac{1}{2}$ years she suffered a third attack of purulent meningitis. Gram-positive cocci were found in the CSF but culture was unsucecssful. She responded rapidly to treatment with antibiotics.

Examination showed an immature and active girl, weight 37·1 kg (25th centile), height 136·3 cm (10th centile). Skull tomography and CSF isotope transport studies did not show anything suggesting a cranio-nasal or cranioaural fistula. There was *x*-ray evidence of ethmoiditis.

Her mother and father (unrelated), both aged 53, are well. Her three brothers (aged 32, 25, and 18 years) and two sisters (aged 31 and 29 years) are well. They have shown no special predilection to infections, except that the youngest brother had one attack of pneumococcal meningitis when he was 16 years old. There was no history of collagen-vascular diseases in the family.

Immunological evaluation

Serum immunoglobulin (IgA, IgG, IgM) concentrations were measured by radial immunodiffusion, using commercial plates (Behringerke, W. Germany), serum IgE by radioimmunoassay (Pharmacia,

Adelaide Children's Hospital,
Department of Paediatrics, University of Adelaide
Y H THONG, senior lecturer
Department of Neurosurgery
DONALD A SIMPSON, director
Department of Molecular Immunology, Scripps Clinic and Research Foundation, La Jolla, California
HANS J MÜLLER-EBERHARD, director

Sweden), total haemolytic complement activity (CH50) by the lysis of sheep red blood cells;[3] lymphocytes and neutrophils were purified from peripheral blood by a one-step gradient centrifugation procedure,[4] lymphocyte transformation by a microtechnique,[5] T-cells as the percentage bearing E-rosettes,[6] B-cells by immunoflorescence,[7] neutrophil chemotaxis by the agarose technique,[8] neutrophil quantitative iodination by a microassay procedure,[9] bactericidal capacity by the killing of *Staphylococcus aureus*.[10] The complement components were measured by immunochemical methods;[11] for this purpose the sera were packed in dry ice and sent by air to Scripps Clinic and Research Foundation, La Jolla, California.

Results

No abnormalities were detected in serum immunoglobulins, lymphocyte function, or neutrophil function (Table 1). There was however, a total absence of serum haemolytic complement activity.

Table 1 *Immunological evaluation of a patient with recurrent bacterial meningitis.*

Tests	*Results*	*Normal range*
Neutrophil function		
quantitative iodination (pmol/10^7 cells/h)	7·6	>3·0
bactericidal capacity (% *S. aureus* killed in 2 hours)	88·3%	75–90
chemotaxis (mm/2h)	1·23	1–20–1·35
Serum immunoglobulins		
IgG (g/l)	6·51	5·59–1·49
IgA (g/l)	2·27	0·54–2·21
IgM (g/l)	1·78	0·27–1·18
IgE (U/ml)	570	64–392
Serum complement		
CH50 (U/ml)	0	95–165
T-cells (%)	60	50–70
B-cells (%)	11	5–15
*Lymphocyte transformation (counts/min)		
phytohaemagglutinin	98 059	>10 000
pokeweed mitogen	79 475	>5 000
concanavalin A	71 230	>10 000

*Counts/min (^{3}H-thymidine uptake in stimulated cultures; resting cultures showed uptake of 2662 counts/min.

Analysis of individual complement components showed a lack of C2 in the patient's serum. The 18-year-old brother showed a lack of C2 in his serum; concentrations of C2 in the mother and eldest sister were intermediate (Table 2). Other family members could not be studied.

Discussion

Several families with C2 deficiency have been described. Although only four members of this family were studied, the findings were sufficient to indicate that the disease was inherited in autosomal codominant fashion, similar to previously reported C2-deficient kindreds. The predilection to collagen-vascular disorders reported in other kindreds,[2] but not observed in this family, is thought to be due either to less efficient clearance of immune complexes, or to the close linkage between immune response genes and genes directing C2 synthesis on the 6th chromosome. Susceptibility to infection is not a feature of this disease, except for one patient reported by Day *et al.*[12] and two others reported by Newman *et al.*[13]

The patient described by Day *et al.*[12] had one attack of pneumococcal meningitis at 5 months, infectious mononucleosis at 7 years, meningococcaemia at 8 years, and numerous febrile episodes and recurrent sore throats. Newman *et al.*[13] reported 3 episodes of recurrent septicaemia in each of two unrelated children with homozygous C2-deficiency. They also found a partial deficiency of alternative pathway. A third patient with similar findings did not have an abnormal predilection to infection, so it cannot be certain that a concomitant dysfunction of the alternative complement pathway is responsible for infective complications. In this regard, our patient has normal function of the alternative pathway since her serum can generate chemotactic factors on interaction with fungi.[14] Furthermore, extensive investigations in our patient did not show other immunological abnormalities to account for the susceptibility to pyogenic meningitis.

Patients with collagen-vascular disorders, recurrent

Table 2 *Serum complement concentrations in a patient with recurrent bacterial meningitis*

Subject	*Age*	*C1q*	*C1r*	*C1s*	*C2*	*C3*	*C4*	*C5*	*C6*	*C7*	*C8*	*C9*	*Factor B*	*Properdin*	*C3b1NA*	*C11NA*	*β1H*
Patient	12	43	48	35	0	1908	541	85	59	79	55	180	170	29	52	15	585
Mother	53	80	56	40	13	1276	610	78	73	84	53	225	216	21	34	17	553
Sister	31	87	56	47	11	1411	716	82	73	59	59	261	270	24	37	21	560
Brother	18	60	52	41	0	1170	604	69	76	63	55	175	144	24	24	11	485
Normal values (μg/ml)																	
Mean		69	49	38	24	1239	601	76	71	55	54	210	190	22	52	15	585
Range		52–85	41–63	31–47	15–34	828–1722	485–863	51–86	45–80	37–70	19–77	123–370	132–258	15–30	28–45	11–29	230–610

infections, or septicaemic episodes, deserve further investigation of complement activity. Immunodeficiencies of this type should also be considered in the differential diagnosis of relapsing meningitis, especially if there is no evidence of a cerebrospinal fluid fistula, whether traumatic[15] or congenital.

References

[1] Müller-Eberhard H J. Complement. Annual review. *Annu Rev Biochem* 1975; **44:** 697–724.

[2] Johnston R B Jr, Stroud R M. Complement and host defense against infection. *J Pediatr* 1977; **90:** 169–79.

[3] Mayer M M. Complement and complement fixation. In: Kabat E R, ed. *Experimental immunochemistry*. 2nd ed. Springfield, Illinois: Thomas, 1971: 133–6.

[4] Ferrante A, Thong Y H. A rapid one-step procedure for purification of mononuclear and polymorphonuclear leukocytes from human blood using a modification of the hypaque-ficoll technique. *J Immunol Methods* 1978; **24:** 389–93.

[5] Thong Y H, Ferrante A. Inhibition of mitogen-induced lymphocyte proliferative responses by tetracycline analogues. *Clin Exp Immunol* 1979; **35:** 443–6.

[6] Scheinberg M, Blacklow N R, Goldstein A L, Parrino T A, Rose F B, Cathcart E S. Influenza: response of T-cell lymphopenia to thymosin. *N Engl J Med* 1976; **294:** 1208–11.

[7] Alexander E L, Sanders S K. $F(ab')_2$ reagents are not required if goat rather than rabbit antibodies are used to detect human surface immunoglobulin. *J Immunol* 1977; **119:** 1084–8.

[8] Thong Y H, Douglas B S, Ferrante A. Abnormal neutrophil chemotaxis in a syndrome of unusual facies, proportionate small stature, and sensorineural deafness-mutism. *Acta Paediatr Scand* 1978; **67:** 383–7.

[9] Thong Y H. Ferrante A. A semi-automated microassay for quantitative leukocyte iodination. *J Immunol Methods* 1978; **20:** 297–9.

[10] Thong Y H, Ferrante A, Ness D. Neutrophil phagocytic and bactericidal dysfunction induced by bilirubin. *Aust Paediatr J* 1977; **13:** 287–9.

[11] Lachman P J, Hobart M J. Complement technology. In: Weir D M, ed. *Handbook of experimental immunology*. 3rd ed. Oxford: Blackwell Scientific, 1978; 5A. 2–8.

[12] Day N K, Geiger H, McLean R, Michael A, Good R A. C2 deficiency: development of lupus erythematosus. *J Clin Invest* 1973; **52:** 1601–7.

[13] Newman S L, Vogler L B, Feigin R D, Johnston R B, Jr. Recurrent septicemia associated with congenital deficiency of C2 and partial deficiency of factor B and the alternative complement pathway. *N Engl J Med* 1978; **299:** 290–2.

[14] Thong Y H, Ferrante A. Alternative pathway of complement activation by *Candida albicans*. *Aust NZ J Med* 1978; **8:** 620–2.

[15] Caldicott W J H, North J B, Simpson D A. Traumatic cerebrospinal fluid fistulas in children. *J Neurosurg* 1973; **38:** 1–9.

Correspondence to Dr Y H Thong, Department of Paediatrics, University of Adelaide, Adelaide Children's Hospital, North Adelaide 5006, South Australia.

Received 18 July 1979