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Hereditary complement factor I deficiency

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Summary

We describe four cases (from three families) of hereditary factor I deficiency, bringing the total number of cases now reported to 23. In one family there are two affected siblings: one has suffered recurrent pyogenic infections; the other is asymptomatic. In the second family, the patient had recurrent pyogenic infections and a self-limiting vasculitic illness; in the third family, the patient suffered recurrent pyogenic and neisserial infections. All four patients had markedly reduced concentrations of C3 in the serum (family 1 propositus: 28%; family 1 asymptomatic sibling: 15%; family 2: 31%; and family 3: 31% normal human serum) which was in the form of C3b. Low IgG_2 levels may occur in primary C3 deficiency, and a reduction in IgG_2 concentration to 1.14 g/l (normal: 1.30–5.90 g/l) was found in the patient from family 2. Using radioligand binding assays, we demonstrated increased binding of C3b to erythrocytes in a patient with factor I deficiency. This C3b could not be cleaved by autologous serum but could be cleaved by normal serum or purified factor I. We review and compare the published cases of C3, factor H and factor I deficiency.

Introduction

Complement factor I (FI) is a serine esterase that acts to control the amplification loop of the alternative pathway of the complement cascade. Hereditary deficiency of FI is a rare autosomal recessive condition. In the absence of FI, the amplification loop of the alternative pathway is activated in an uncontrolled fashion, so that there is consumptive loss of complement C3.[1–4] Secondary depletion of C3 is also caused by genetic deficiency of complement component factor H (FH), which is a cofactor for FI. The study of these hereditary deficiencies is important because of the evidence that they provide in relation to the roles of the complement system *in vivo*. Furthermore, it was the investigation of the physiology of the complement system in the first case of FI deficiency[1–4] that generated much of the early evidence for the existence of the amplification loop of the alternative pathway.[5]

The clinical effects of C3, FI and FH deficiency are similar: a propensity to suffer recurrent pyogenic infections and an increased incidence of glomerulonephritis and SLE-like illness. The clinical consequences of C3 deficiency reflect the role played by the complement system in the opsonization of pathogens and the clearance of immune complexes.[6] Although there are subtle differences in the effects

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of these three conditions on the complement system, the predominant influence on the clinical outcome in all three states is that of C3 deficiency.

To date, 19 patients with FI deficiency have been reported.[7–19] We report an additional four patients from three families. In one family, there were two homozygously affected siblings; one of whom suffered recurrent pyogenic infections, the other being healthy. In the other two families there were single, homozygous, symptomatic individuals. We review the clinical features of FI deficiency, and then compare them with the clinical consequences of FH and C3 deficiencies. The clinical features of all the reported cases of these hereditary deficiencies are tabulated (see Table 1) and their pathogenesis and treatment are briefly discussed.

Patients

Family 1

A 14-year-old boy presented with a history of recurrent pyogenic infections that began at the age of 18 months. At this time he developed a septic arthritis of the left shoulder from which *Staph. epidermidis* was cultured. At the age of 5 years he suffered orbital cellulitis, and over the next 5 years he had recurrent episodes of sinusitis. When 8 years old, an abscess on the side of his neck was drained. At the age of 13 he had a single episode of meningococcal meningitis. He has subsequently had a number of minor respiratory tract infections. Physical examination was unremarkable. There was no family history of immunodeficiency or autoimmune disease, and no consanguinity, although both parents originate from western Scotland. He has one sibling, a sister who is 5 years older, who has neither suffered from any major episodes of infection with pyogenic organisms, nor had recurrent sinusitis or otitis media.

Investigation of both siblings revealed a normal full blood count and basic biochemistry profile. The immunoglobulin concentrations of both siblings were within the normal ranges: the affected male's values were: IgG 10.5 g/l (normal: 7.2–16.2); IgA 1.3 g/l (0.8–3.9); IgM 2.3 g/l (0.5–3.5); his sister's values were: IgG 9.5 g/l (7.2–16.2); IgA 1.1 g/l (0.8–3.9); IgM 1.5 g/l (0.5–3.5). The IgG subtype concentrations gave no evidence of selective isotype deficiency: the affected male's concentrations were: IgG_1 9.05 g/l (3.2–10.2); IgG_2 2.97 g/l (1.2–6.6); IgG_3 1.25 g/l (0.2–1.9); IgG_4 0.20 g/l (0.10–1.3); the IgG subtype levels of the asymptomatic sister were as follows: IgG_1 10.05 g/l (3.2–10.2); IgG_2 2.73 g/l (1.2–6.6); IgG_3 1.55 g/l (0.2–1.9); IgG_4 0.20 g/l (0.10–1.3). Antinuclear antibodies (ANA) (measured by indirect immunofluorescence on Hep-2 cells) and rheumatoid factor (measured by Latex agglutination) were not detected. His complement system was investigated together with that of all four family members (see Table 2). The results demonstrate the diagnosis of FI deficiency in the patient and in his asymptomatic elder sister: FI was undetectable in both siblings, as was factor B (FB); there was no detectable alternate pathway activity (APH50); and both FH and properdin levels were reduced. Both parents had approximately half the normal concentration of circulating FI.

The patient is being treated with prophylactic phenoxymethylpenicillin, 250 mg bd. He was vaccinated with Pneumovax and mounted a significant IgG_2 response: pre-immunization 1:16; post-immunization 1:110; control 1:160 (measured by Dr Kumaratne, Immunology Dept, Dudley Road Hospital, Birmingham). He is now aged 19 years and has had no further significant infective episodes. His sister, who is 24 years old, also remains well.

Family 2

The affected male in this pedigree has suffered from recurrent otitis media since infancy. He had one episode of idiopathic keratitis when aged 5 years. Because of recurrent sinusitis, surgery to the nasal septum was performed at age 14 and it was noted that he was allergic to both penicillin and sulphonamides. When he was 16 years old, he suffered four bouts of left-sided bronchopneumonia together with sinusitis. *Str. pneumoniae* and *Staph. aureus* were cultured from the sputum. The following year a bronchogram was performed, no lesion was demonstrated, but an episode of bronchopneumonia was precipitated. When aged 20, a sixth episode of bronchopneumonia occurred. Five years later, he had a self-limiting illness characterized by hepatitis, pneumonitis, myositis, possible meningitis, and purpura, with histological evidence of a microangiopathic vasculitis on skin biopsy. During the next ten years, he had five additional episodes of bronchopneumonia.

At the age of 36 he was fully investigated, and the diagnosis of FI deficiency was established. He had a normal full blood count and biochemistry. His ANA and rheumatoid factor were negative. The concentrations of immunoglobulin isotypes were within the normal ranges, however, analysis of IgG subtypes: IgG_1 11.49 g/l (3.55–11.25); IgG_2 1.14 g/l (1.30–5.90); IgG_3 0.44 g/l (0.15–1.05); IgG_4 0.54 g/l (0.10–1.10), indicated that the IgG_2 concentration was diminished. Analysis of the complement system confirmed the diagnosis of FI deficiency (see Table 3). Additional family members were also studied (see Figure 1) indicating the inheritance of the trait throughout the family. This family is Swiss/German in origin, there is no known consanguinity. The

Table 1a Hereditary Factor I deficiency: twenty-three patients from nineteen families (separated by lines)

Patient	Age (years)	Sex	Nationality Race	Consanguinity	Age of onset	Infections	Other complications	Notes	Reference
1	25	M	USA	?	1 year	Haemorrhagic measles	Klinefelter's syndrome XXY	Became C3 Coombs negative for 14 days and had	(1) (2)
			?			Recurrent otitis media Recurrent sinusitis Inguinal abscess		undetectable C3b and 17 days after infusion of normal plasma C3 and C5 levels raised for 12	(3)
						Auricular abscess: *C. diphtheriae* Septicaemia ×2: *Str. pyogenes* *N. meningitidis* Pneumonia: *H. influenzae*	Urticaria	days but FB levels maintained for only 3 days after infusion of purified FI	(4)
2	11	F	English Caucasoid	no	4 months	Meningitis ×4: *Str. pneumoniae* ×1 *N. meningitidis* ×2 Otitis media			(7)
3	?	F	USA ?	?	?	Meningitis ×3 *H. influenzae* b *N. meningitidis*			(8)
4	?	F		?	3 months	Pneumonia ×1			
5	3	M	Germany		6 months	Gastroenteritis Recurrent otitis media Septicaemia UTI ×3	IgM rheumatoid factor positive ANA negative	Abnormal FH mobility (by immunoelectrophoresis) probably due to its binding to C3b Infusion of plasma (FFP): C5 and FH elevated above pre-infusion levels for up to 1 month FB increased for 6 h only No complications after 22 infusions of FFP	(9)
6	28	M	Canada Caucasian	No	Infancy	Recurrent otitis, bronchitis, and mastoiditis Pneumonia ×4 Pleural empyema: *Str. pneumoniae* Bronchiectasis Meningitis	Serum sickness-like illness following the administration of penicillin	5 of 10 siblings died in infancy 3 from sepsis, ?FI status IgM rheumatoid factor (1:1280) ANA negative	(10)

Table 1a *(continued)*

Patient	Age (years)	Sex	Nationality Race	Consanguinity	Age of onset	Infections	Other complications	Notes	Reference
7	19	F	Denmark Caucasoid	No	19 years	Otitis media Meningitis: *N. meningitidis* GpB Herpes zoster			(11) (12)
8	15/12	F	USA ?	?	3 weeks	Septicaemia: *Str. pneumoniae* Pneumonia: *Str. pneumoniae* Otitis media ?Osteomyelitis	low IgA (0.36 g/l)	Infusion of FI: C3 and FB increased for 4 days FH and CH50 increased for 14 days FI remained undetectable	(13)
9	9	?	France ?	?	?	Recurrent bronchitis, otitis media and mastoiditis		Reduced erythrocyte CR1 Normal range 300–1320	(14)
10	?	?	France ?	?	9 years	Arthritis: septic ?agent		Reduced erythrocyte CR1 Normal range 300–1320 patients: 10–115; 11–182	(14)
11		?	France ?		11 years	Arthritis: *N. meningitidis*		Defective CR1- and CR3-dependent phagocytosis	
12	37	M	? Caucasoid	No	Childhood	Recurrent otitis, sinusitis Pneumonia ×8 Meningitis ×5: *N. meningitidis* (GpB ×1, W135 ×1) Septicaemia with DIC ×2		Treatment with FFP: C3 increase 16 days Native FB increase 4 days Fall in C4 and rise in C4d duration – 2 days FI half-life estimated 29 h Anaphylaxis with 8th and 9th FFP infusions	(15)
13	37	F	Caucasoid	No	37 years	Fatal systemic vasculitis: cutaneous leucocytoclastic lesions Haematuria and proteinuria Deep venous thrombosis Perivenous encephalomyelitis (diagnosed at post-mortem)	Vasculitic illness followed the administration of penicillin for pharyngitis Cryoglobulinaemia ANA not reported	Very low, but detectable levels of FI, C3d and C4d also detectable (?from blood transfusion)	(15)
14	27	M	Tunisian	No	Childhood	Recurrent otitis media and cutaneous abscesses			(16)
15	?	M					Asymptomatic		

16	20	F	France ?Caucasian	Yes (second cousins)	17 months	Recurrent pharyngitis Meningitis ×3: *N. meningitidis* (GpC ×1) *N. meningitidis* (untypable ×1) Pneumonia ×1	(*Str. pneumoniae*) ?FI status	Older brother died age 12 of meningitis	(17)
17	12	F	France Turkish	Parents from same village	4½ years	Pneumonia ×2 Meningitis: *H. influenzae* type b		Two siblings both well	(17)
18	4	M	USA Caucasian	?	?	Recurrent sinusitis and pulmonary infections	Urticaria	IgA <6 mg/dl (35–209) some FI detected 2.6% (46–159) C3 27 mg/dl (83–177), FB <12 mg/dl (17–42)	(18)
19	28	F	Greek	?	24 years	Aseptic meningitis ×11	Sulphonamide allergy	Weakly positive ANA 1:40 to 1:80 No anti-dsDNA antibodies	(19)
20	15	M	Scottish Caucasoid	No	18 months	Septic arthritis: *S. epidermidis* Orbital cellulitis, bronchitis Recurrent otitis media and sinusitis Cutaneous abscess Meningitis: *N. meningitidis*		ANA negative	
21	18	F						Asymptomatic	
22	36	M	Swiss	No	Childhood	Recurrent otitis media, sinusitis bronchopneumonia ×10 (*Str. pneumoniae* *H. influenzae*)	Sulphonamide/ penicillin Allergy one episode of a multisystem inflammatory illness ?vasculitic	ANA negative	
23	6	M	Spanish	Parents from nearby villages	3 weeks	Cutaneous sepsis (*Staph. aureus*) Meningitis ×4: *N. meningitidis* ×3 *Str. pneumoniae* ×1 Conjunctivitis Otitis media, enteritis, septicaemia Herpes zoster		low IgG_2 1.14 g/l (1.30–5.90) ANA negative	

Table 1b Reported human C3 deficiency: twenty-two patients from fifteen families (separated by lines)

Patient	Age (years)	Sex	Nationality Race	Consanguinity	Onset of infections	Infections	Other complications	Notes	Reference
1	15	F	South Africa Caucasoid	Yes	Infancy	Pneumonia ×14	Erythema gyratum perstans	Partial C3 gene deletion	(25)
						Meningitis: *N. meningitidis*	Sweet's syndrome	No blood neutrophilia during infection	(26)
						Otitis media			(27, 28)
2	11	F	USA ?	Adopted	1st year	Otitis media: *H. influenzae* b UTI: *E. coli* Septicaemia: *Str. pneumoniae*	MCGN	Normal leucocytosis to infection Normal Rebuck skin window	(29) (30)
3	4	F	South Africa Caucasoid	No	1 year	Meningitis: *Str. pneumoniae* ×3 Lobar pneumoniae: *Str. pneumoniae* Died age 7 yr 6 mths		Necropsy: purulent meningitis with polymorphs + + in subarachnoid space; peripheral lymphoid tissues: barely discernible germinal centres; low IgG levels (3.8–6 g/l)	(31)
4	3	M	USA Caucasoid	Yes	–	No	Maculopapular rash Arthralgia wrist, fever	Illness resolved following whole blood transfusion	(32)
5	5	F	USA	?	5 months	Pneumonia Septic arthritis Otitis media, febrile convulsions		Blunted leukocytosis to infection	(33)
6	13	F	Lebanon Palestinian	?		Frequent earache Sore throat	Proteinuria Microhaematuria		(34)
7	7	F			6½ years	Peritonitis: *Str. pneumoniae*	Proteinuria Microhaematuria	Left renal artery stenosis	(34)
8	5	M			3 years	Peritonitis	Proteinuria	Heterozygous sibling MCGN	(34)
9	19	F	Japan	Yes	'early childhood'	Bronchitis	SLE-like symptoms age 16: erythematous rash, fever, arthralgia, photosensitivity, ANA-ve, LE-ve		(35)
10	14	F				No	SLE-like symptoms age 10: photosensitive facial rash, arthralgia, ANA-ve, LE-ve		(35)
11	10	F	Chinese	No	8 months	Pneumonia Septic arthritis Otitis media: *H. influenzae*	Rash and arthralgia during infection	Normal leucocytosis during infection	(36)
12	26	F	Dutch	?	7 months	Meningitis: *N. meningitidis*		Low IgG_2 1.48 g/l (3.80 ± 1.10)	(37)

						Meningitis: *Str. pneumoniae* 'sepsis': *S. aureus*			
13	19	F			1¾ years	Meningitis: *Str. pneumoniae* Otitis media	Transient maculopapular rash during infectious episodes	Low IgG_2 0.11 g/l (3.80 ± 1.10)	
14	16	F			8 months	Osteomyelitis Otitis media	Transient maculopapular rash during infectious episodes MCGN type I	Low IgG_2 0.44 g/l (3.80 ± 1.10) Administration of FFP of no benefit	(64)
15	7	M	Laos	No	5 months	Lobar pneumonia Meningitis: *Str. pneumoniae* × 2	MCGN	Acute administration of FFP not associated with renal deterioration	(38) (39)
16	12	F	Kuwait	?	–	Nil	Microhematuria Nephrotic syndrome Renal failure MCGN Type I		(40)
17	6	M	Brazil	Yes	3 months	Meningitis: *N. meningitidis* × 3 Bronchopneumonia × 4 Otitis media, osteomyelitis × 2		Normal leucocytosis to infection	(41)
18	10	M	England	Yes		Otitis media URTI: *Str. pyogenes*	Transient erythema multiforme at time of infection		(41)
19	23	M	Japan	Yes	4	Meningitis	IgA nephropathy		(42)
20	14	F					Lupus-like illness	First cousin of patient 19	(42)
21	19	M	N. Zealand/ Israel	?	Childhood	Pneumonia Meningitis: *N. meningitidis*			(43)
22	7	F						*Asthma, rhinitis, otherwise healthy*	
Dysfunctional C3 molecules									
1	47	F	Swedish	No		Recurrent otitis media Meningitis *N. meningitidis* Gp Y		Weak ANA, IgG and IgM at dermo-epidermal junction	(50)
2	42	F				None	SLE	+ve ANA, anti-dsDNA antibody, anti-centromere antibody	

Table 1c Hereditary Factor H deficiency: twelve patients from six families

Patient	Age (years)	Sex	Nationality Race	Consanguinity	Age of onset	Infections	Other features	Notes	Reference
1	8/12	M	Indian	Yes (first cousins)	8 months	Otitis media: *H. influenzae*	Haemolytic-uraemic syndrome (HUS)	Very low factor H detected (6% NHS) Renal biopsy characteristic of HUS	(44)
2	3	M					Asymptomatic		
3	5	M	Algerian	Yes (first cousins)	14 months	Recurrent otitis and bronchitis followed by haematuria	Glomerulonephritis MCGN-like	FH 12% NHS in both cases renal biopsy appearance similar in both: intramembranous dense deposits detected atypical immunofluorescence (IF): anti-C3 staining in mesangium and capillary walls, not in the basement membrane H antigen and C5b-9 neoantigens in the areas of C3 staining	(45)
4	6/12	M			4 months	Otitis media and bronchitis Septicaemia: *E. coli* UTI: *Proteus sp.* Persistent haematuria	Glomerulonephritis MCGN-like		
5	?	F	Spain	No	?	*N. meningitidis*	MCGN	No factor H antigen detectable in all sibs Reduced C5 (<10% NHS) and C9 (10% NHS)	(46)
6	?	F			?	*N. meningitidis*	MCGN	No details of renal biopsy given	
7	?	F			?		MCGN	All ANA negative	
8	?	F	Italy	Yes	?	None	Asthma Haematuria	FH undetectable in all 3 sibs Heterozygous C2 deficiency	(47)
9	11	F			11 years		SLE with nephritis Anti-dsDNA antibodies	Heterozygous C2 deficiency Renal biopsy: diffuse proliferative nephritis 6 of 25 glomeruli with crescents C3 (3+) and IgG (1+) in mesangium by IF Responded to prednisolone (2 mg/kg/day)	
10	?	M			?		Asymptomatic	Normal C2	

11	15	F	Danish ?	No	10 years	Meningitis × 2: *N. meningitidis* Gp B		No detectable FH Depressed C5 (7% NHS) and C7 (< 0.5% NHS) ?C7 deficiency too	(48)
12	49	F	Netherlands	?	?	Meningitis: *N. meningitidis* Gp X	SLE/lupus-like illness	No details of autoantibodies	(49)
Partial factor H deficiency									
1	17	M	USA Polish	?	11 years		Henoch-Schönlein purpura Thrombocytopenia and splenomegaly	Three other asymptomatic family members	(51) (52)
2	?	F	USA Anglo-Irish	?	63 years	?Recurrent UTIs	Hypertension		(52)
3	38	M		30 years			IgA nephropathy leading to end-stage renal failure	Diagnosis on renal biopsy	
4	33	F		36 years			IgA nephropathy (mild)	Renal biopsy performed (sister of patient 2)	
5	26	M		26 years			Proteinuria	Brother of patient 2	
6	2	F	USA ?	No	18 months	Recurrent respiratory tract infections	Haemolytic-uraemic syndrome × 3	Died age 2 yrs Null allele at C4A and C4B Abnormal C3 variant with reduced total C3	(53)

Table 2 Complement profile of family 1

	FI	FH	FB	P	APH50
Mother	41	96	71	51	50
Father	74	155	71	52	45
Propositus	–	46	–	38	–
Sister	–	42	–	29	–
	C2	C3	C4	C5	CH50
Mother	84	84	71	137	92
Father	96	99	147	91	102
Propositus	77	28	60	99	–
Sister	90	15	105	48	–

All results expressed as % normal human serum.
-, undetectable.

Table 3 Complement profiles of the propositi from family 2 and family 3

	FI	FH	FB	P	C4BP	APH50	FD100
Propositus 2	–	53	17	34	107	–	82
Propositus 3	–	42	9	38	72	–	68
	C2	C3	C4	C5	C7	CH50	
Propositus 2	ND	31	159	53	30	47	
Propositus 3	ND	31	124	34	36	40	

-, undetectable; ND, not determined.
All results expressed as % normal human serum.

patient is now 43 years old and is well apart from occasional febrile illnesses which respond rapidly to the administration of antibiotics.

Family 3

A 6-year-old presented with a history of recurrent pyogenic infections which began at the age of 3 weeks with a cutaneous abscess and omphalitis due to *Staph. aureus*. At 3 months, he developed a second abscess, and at 6 months he started having persistent folliculitis. When 4 months old, he became septicaemic with *Str. pneumoniae*, and at 9 months he had a further pyrexial illness. At 14, 15 and 16 months of age he had an abscess on the right cheek, enteritis, and purulent conjunctivitis, respectively. When 19 months old he suffered a pyrexial illness with erythematous rash that responded to penicillin. Four months later, he had two episodes of meningitis in rapid succession; the first due to *N. meningitidis* and the second due to *Str. pneumoniae*. The following month he had otitis media and then septicaemia with *Str. pneumoniae*. Between the ages of 3 and 6 years the patient suffered from otitis media, bronchitis, enteritis, purulent pharyngitis, and aphthous stomatitis. When 6 years old, he had an episode of meningococcal septicaemia after which complement studies were performed (see Table 2) and the diagnosis of FI deficiency was made. The immunoglobulin concentrations were: IgG 8.24 g/l (6.86–14.9); IgA 1.5 g/l (0.45–3.09); IgM 0.74 g/l (0.41–3.00) and IgG subtypes were: IgG_1 8.07 g/l (3.55–11.25); IgG_2 2.67 g/l (1.30–5.90); IgG_3 0.26 g/l (0.15–1.05); IgG_4 0.26 g/l (0.10–1.10). The concentration of FI in other family members is shown in Figure 2. Although the propositus and his parents now live in Switzerland, the family was originally from northern Spain, and the parents of the FI-deficient boy were from neighbouring villages. There is no history of consanguinity, however.

The patient was vaccinated with Pneumovax and

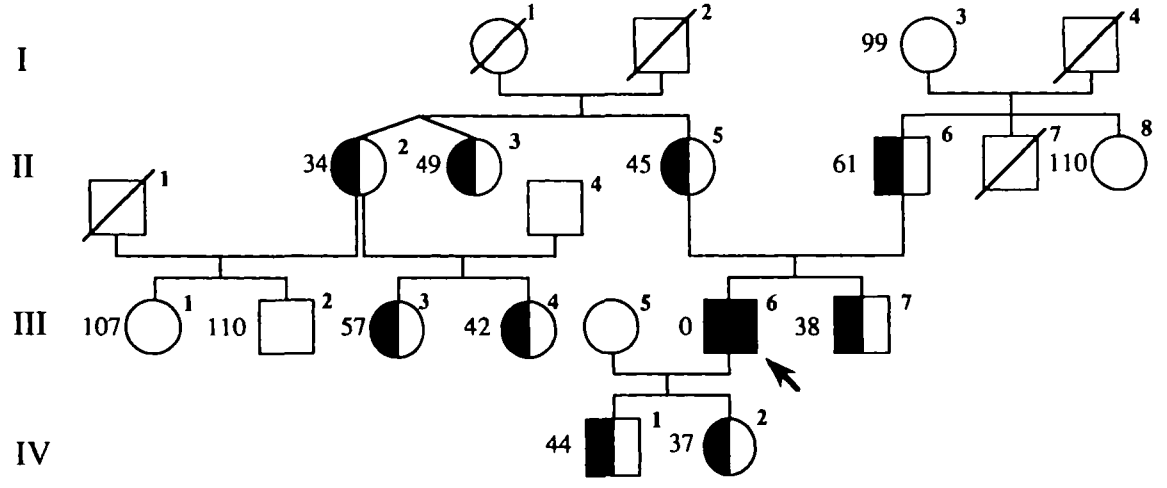

Figure 1. The pedigree shows the inheritance of factor I deficiency in the family of Swiss/German origin (family 2). The propositus is marked with an arrow. The number to the left of the individuals is the factor I concentration in the serum of that individual expressed as a percentage of the value of normal human serum: normal range 75%–135%.

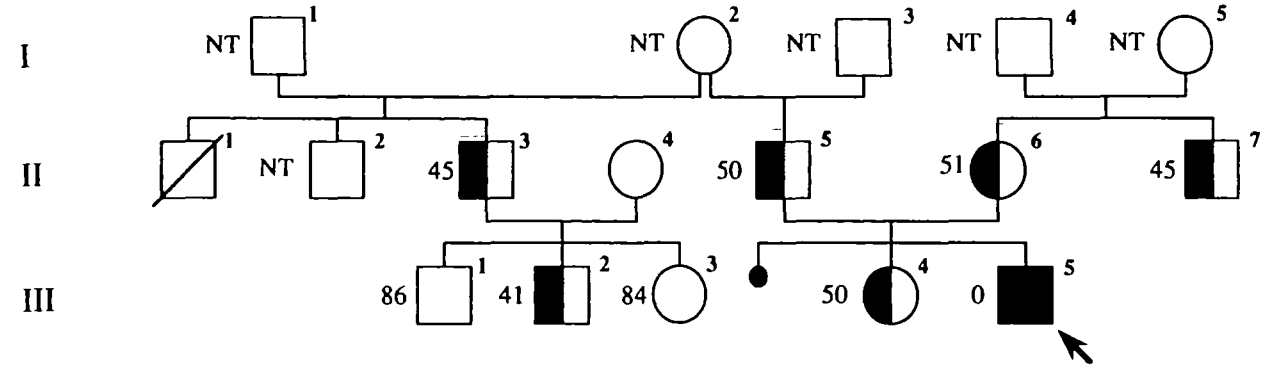

Figure 2. The pedigree shows the inheritance of factor I deficiency in the family of Spanish origin (family 3). The propositus is marked with an arrow. The number to the left of the individuals is the factor I concentration in the serum of that individual expressed as a percentage of the value of normal human serum: normal range 75%–135%. NT signifies an individual whose FI concentration was not tested.

maintained on prophylactic penicillin for 3 years. During this period he had intermittent bouts of bronchitis and sinusitis, and when 8 years old, varicella-zoster. He is now 15, and having withdrawn prophylactic penicillin of his own volition for 3 years, has remained relatively well with occasional pyrexial illnesses but no septicaemic episodes.

Methods

Complement assays

Antigenic and functional assays

Serum concentrations of the complement proteins were assayed by radial immunodiffusion using polyclonal antisera (sheep anti-C2, anti-C3, anti-C4, anti-C5, anti-FI, anti-FH, and anti-properdin: The Binding Site, Birmingham). Functional complement assays were performed as follows:[20] classical pathway activity (CH50) was assessed using a haemolytic assay with sheep red blood cells sensitized with rabbit antibody (Tissue Culture Services, Buckingham), in a 1.5% CFD/agarose gel (Oxoid, Basingstoke); alternative pathway activity (APH50) was measured by haemolytic assay with guinea pig erythrocytes (Tissue Culture Services, Buckingham) in a 1.5% agarose gel in the presence of 7 μM $MgCl_2$ and 10 μM ethyleneglycol tetraacetic acid (EGTA). The FD100 is an assessment of factor D (FD) activity. It was measured in the same way as APH50, except that the guinea pig erythrocytes were suspended in FD-depleted (by affinity chromatography) serum. The investigation of the state of circulating C3 in the FI-deficient members of family 1 was carried out by crossed immunoelectrophoresis according to the method of Laurell, as described in reference 20.

Assays for cell-bound C3 and CR1

The binding of C3b and its degradation products on the red cell surface was analysed by radioligand binding assay as previously described.[21] Three anti-C3 monoclonal antibodies were used (clones 3, 4 and 9, kindly provided by Prof. P. Lachmann, Cambridge) which recognize C3d, C3c and C3g, respectively.[22] Erythrocyte CR1 numbers were also measured by radioligand binding assay using the monoclonal antibody E11 (kindly provided by Dr Nancy Hogg, ICRF, London). The binding of this antibody to the receptor is not affected by the ligation of CR1 with C3b.[23]

The purified FI and FH reagents, used in the ligand binding studies, were prepared by affinity chromatography using specific monoclonal antibodies coupled to cyanogen-bromide-activated Sepharose (Pharmacia): anti-FI: MRC OX21; anti-FH: MRC OX23 (Serotec, Oxford).[24]

Results

Complement estimation

The complement profiles of the four homozygously affected patients from the three families are given in Tables 2 and 3. In none of them was FI detected in the circulation. The complement profiles of these patients were similar. They had very low or undetectable levels of factor B (FB), and no detectable alternative pathway activity (APH50). The C3 concentrations were also very low. Crossed immunoelectrophoresis of serum from the two affected siblings from family 1, indicated that 90% of the C3 was in the form of C3b (data not shown). The reduced concentrations of FH and properdin in all the propositi to approximately one half of their

normal value have been documented in all nine cases of FI deficiency in which these components have been assessed.[4,9,10,13,15,17,19] In one report,[15] normal FH and properdin levels were probably the result of a prior infusion of blood. Reduced levels of the terminal pathway components C5 and C7 were found in the affected individuals from families 2 and 3 and the sister of the propositus from family 1 (C5 only). A reduction in C5 has been reported in seven previous cases,[5,9,10,13,15,17] and a reduction in C7 in four cases.[5,10,17] In none of the reports in which these two complement components were measured were normal values recorded.

The results of the radioligand binding studies performed on family 1 (see Table 4) indicate that the amount of C3b present on the erythrocyte surface was increased ten-fold in both homozygotes, as demonstrated by the binding of the two monoclonal antibodies to the C3d and C3c portions of C3b. No increase in binding was observed in the heterozygously-affected parents. The antibody specific for C3g, clone 9, recognises a neoantigen on C3 revealed by the action of FI. No significant binding was found with this antibody to erythrocytes from normal or affected individuals.

Following the incubation of erythrocytes from the FI-deficient patient with autologous serum, there was no change in the pattern of binding observed with the three different anti-C3 monoclonal antibodies (see Figure 3). The incubation of the patient's erythrocytes with either normal serum, purified FI, or a mixture of FI and FH, resulted in a similar outcome as regards monoclonal antibody binding: an increase in clone 9 binding (indicating conversion of C3b to iC3b and C3dg by FI); no apparent change in the binding of clone 3 (which binds to epitopes expressed in both C3b and in its breakdown products that remain surface-bound); but a fall in clone 4 binding (this antibody binds C3c which is cleaved from iC3b by FI and released into the fluid phase).

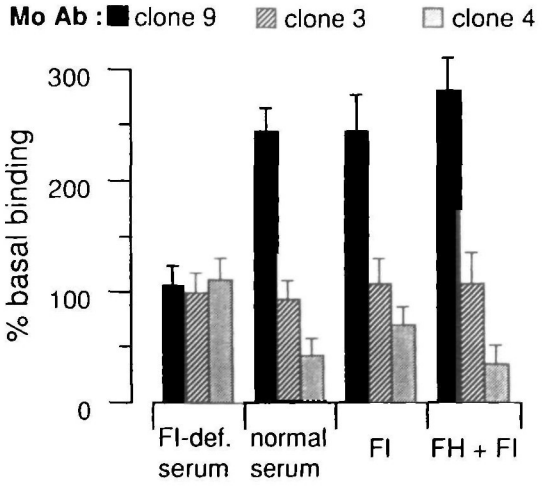

Figure 3. The treatment of erythrocytes from the propositus of family 1 with either normal serum or purified factor I (+/− factor H) resulted in a 2–3 fold increase in the binding of the monoclonal clone 9 (which binds to neoepitopes in C3g). The concentration of factor I used was 10 μg/ml and the concentration of factor H used was 50 μg/ml. There was no change in clone 3 binding (which binds to C3b and its degradation products), and a fall in clone 4 binding (which binds to the C3c portion of C3).

Review of the cases of hereditary FI, FH and C3 deficiencies

All the reported cases of hereditary FI, FH and C3 deficiencies are outlined in Table 1. There are 22 patients with homozygous C3 deficiency,[25–43] 23 with FI deficiency,[1–4,7–19] and 12 who lack FH.[44–49] Of these, all but one case of homozygous C3 deficiency is symptomatic;[43] two cases of FI[16] (family 1, this report) and FH deficiency[44,47] are asymptomatic. In addition, we tabulate one family in which complete C3 deficiency has resulted from the inheritance of one null allele and one dysfunctional molecule;[50] six instances of partial FH deficiency are also summarized.[51–53]

Discussion

The most consistent clinical feature of these three inherited complement deficiencies is susceptibility to infection. This is predominantly due to pyogenic organisms and *Neisseria meningitidis*. Infection with *N. meningitidis* was documented in 11/22 cases of FI deficiency, in 4/12 cases of FH deficiency, and in

Table 4 Assessment of C3 and CR1 numbers on erythrocytes (family 1)

C3 fragment... Monoclonal antibody...	C3d (clone 3)	C3c (clone 4)	C3g (clone 9)	CR1 (E11)
Mother	41	59	15	908
Father	74	52	24	645
Proband	475	573	29	311
Sister	516	621	27	339
Normal	45	93	31	300–1300[a]

[a]The number of erythrocyte CR1 is subject to a genetic influence, and hence an absolute normal range has limited meaning.

4/22 cases of C3 deficiency. The efficacy of complement as an opsonin is indicated by the recurrent pyogenic infections sustained by C3-deficient individuals. In both FI and C3 deficiency, defective opsonization and killing of microbes has been demonstrated with phagocytes from affected individuals using *in vitro* assays.[4,14,37,39] Moreover, the defective opsonization and bactericidal activity of leucocytes were improved, *in vitro*, if either infusions of FFP were given,[39] or the missing complement component was replaced, either FI[4] or C3.[37]

Isolated hereditary deficiency of the terminal pathway components increases susceptibility to neisserial infection, implying that the membrane attack complex is important in the eradication of these organisms.[54] The increased incidence of neisserial infections in C3 deficiency is presumably due to the reduced efficiency of the terminal pathway. Low C5 and C7 levels were found in the propositi from families 2 and 3 in this paper, confirming observations from other reports of FI deficiency.[5,9,10,13,15,17] A reduction in the concentration of C5 has been reported in nine of the ten symptomatic cases of FH deficiency,[45–48] and was normal in only one case.[44] In this latter case there was a low level of circulating FH detected, and no instance of neisserial infection was recorded in the propositus. C5 is consumed in FH and FI deficiency because of the C5 convertase activity (C3bBbC3b) derived from the alternative pathway C3 convertase (C3bBbP) which is present in excess. An additional factor in the predisposition of these patients to infection may be that opsonization of the pathogens by antibody and C3 to form immune complexes facilitates their delivery to the splenic macrophage system.[55] Therefore, C3-, FH- and FI-deficient individuals may be functionally hyposplenic. The infections typically commence in early childhood: the median age of the first pyogenic infection in FI deficiency was 17 months; in FH deficiency it was 14 months; and in primary C3 deficiency it was 8 months. Evidence from the three symptomatic cases presented in this paper suggests that the frequency of infection declines with age. A possible explanation of this phenomenon is that as the immunological memory of the adaptive immune system expands with increasing age, so the role of the innate immune system becomes less important.

It is apparent from the data in Table 1 that there is a marked contrast in the incidence of renal disease in FI deficiency compared to the incidence in C3 and FH deficiencies. Glomerulonephritis has not been described in any of the reported cases of FI deficiency, including the four examples reported in this paper. In C3 and FH deficiencies, there is frequent evidence of some renal involvement. FH deficiency seems to have the strongest association with renal disease. From a total of 12 patients, seven had definite nephritis: five of these had mesangiocapillary glomerulonephritis (MCGN),[45,46] one had the haemolytic–uraemic syndrome,[44] and another had crescentic nephritis[47] (this patient also had heterozygous C2 deficiency). In C3 deficiency, glomerulonephritis was recorded in 8/20 patients and in four of these was of MCGN-type.[30,37–39,40] In two of these cases,[37,40] it was specified to be type 1 MCGN, of which the characteristic feature is subendothelial deposits. The exact mechanism by which nephritis develops in these two C3 deficiency states is unclear. That C3 and FH deficiency patients suffer an MCGN-like nephritis is interesting because of the association of this disease with the C3 depletion found in conjunction with a C3 nephritic factor. The C3 nephritic factor is usually associated with type II (dense-deposit) MCGN. The association between C3 deficiency and MCGN-like nephritis is further strengthened by the observation that dogs with hereditary C3 deficiency develop a nephritis whose histological pattern is that of MCGN.[57]

The absence of FI produces marked abnormalities of the complement system (see Table 5 for a comparison of the effects of C3, FH and FI deficiency), and yet has not been associated with glomerulonephritis. Thus there is no straightforward relationship between the derangement of the complement system as measured *in vitro* and the predisposition to disease. In FI deficiency, only three cases of 'immune complex' illnesses have been described; one being the multisystem inflammatory disorder that occurred in the propositus from family 2. Another patient succumbed to a fatal vasculitic syndrome,[15] and the third had a serum sickness-like syndrome following the administration of penicillin.[10] The association of immune complex disease with recurrent infection raises the possibility that the two are related. Recurrent infections, by stimulating an acute-phase response, may theoretically exacerbate an immune-mediated inflammatory process; alternatively, microbial pathogens may act as the antigenic source for immune complex disease. In one case of FH deficiency,[45] in which there was MCGN-like glomerulonephritis, recurrent episodes of otitis media and bronchitis were followed by episodic haematuria. In six patients with hereditary C3 deficiency, transient maculopapular skin rashes have developed during infective episodes.[25,32,36,37,41] In one study[37] circulating immune complexes (identified by C1q binding assay) were present at the time when a rash developed in two patients. Skin biopsy revealed local deposition of IgG, IgM, C1q, but not C3, by immunofluorescence. It is of note that in the three cases of FI deficiency in which 'immune complex' type illness developed (the case from family 2, and those reported in references 10 and 15) the illness followed the administration of antibiotic. The complement

system is also an important effector mechanism in the inflammatory response. It is therefore possible that if some residual C3 activity remained the consequences of immune complex deposition/formation would be aggravated. In one instance of FH deficiency,[45] in which there was some FH antigen detected (12% normal), two siblings both developed MCGN-like glomerulonephritis. Renal biopsies were performed and subjected to immunofluorescence. The results indicated that C3 was deposited in the mesangium and capillary walls, and that FH and C5b-9 neoantigens were present in a similar distribution to C3. The localization of C5b-9 neoantigens suggests that there was formation of the C5 convertase and that complement was playing an active part in the inflammatory process.

There may be an increased incidence of nephritis in cases of partial (heterozygous) complement deficiency. Two families are summarized in Table 1 in which partial FH deficiency occurs with IgA nephropathy.[51,52] There is one instance of IgA nephropathy in a patient with homozygous C3 deficiency.[42] No disease has been associated with heterozygous FI deficiency. In the three families reported, there were no unusual clinical problems in any of the heterozygous FI-deficient individuals. In addition, in one family in which partial FI deficiency occurred in conjunction with C1-inhibitor deficiency,[57] the clinical manifestations of the C1-inhibitor deficiency were not altered by the coexistence of heterozygous FI deficiency.

A reduced concentration of IgG_2 was found in the propositus from family 3. Low IgG_2 concentrations were found in one family to be associated with homozygous C3 deficiency[37] together with a reduced antibody response to pneumococcal capsular polysaccharide (which is IgG_2–dependent).[58] Antibody isotypes have not been studied in FH deficiency, and in family 1, one of the cases of FI deficiency reported here, normal concentrations of IgG_1 and IgG_2 were measured together with a normal IgG_2 response to pneumococcal capsular polysaccharide. In one systematic investigation of IgG subclasses in complement deficiencies,[59] lower mean levels of IgG_2 were found in primary C3 deficiency compared to normals, and a marked reduction in IgG_4 was a consistent finding in classical pathway and C3-deficiency states. Using bacteriophage ϕX174 as a test antigen, two C3-deficient patients produced normal titres of IgM following primary and secondary immunization, but failed to make an isotype switch to IgG when the antigen was used at low dose.[60] In C3, FI, and FH deficiencies, normal antibody responses to antigens such as tetanus toxoid, diptheria, and pertussis vaccine have been recorded.[37,48] In one study[61] which included one FH-deficient pedigree in Italy, high titres of antibody against meningococcal polysaccharides A and C were observed, presumably as a consequence of natural infection. However, only a modest response was then generated by immunization with the meningococcal vaccine, Menpovax A+C.

The mechanism by which five patients (one without C3, and two without FH and FI) are asymptomatic is not known. The explanation presumably lies in the fact that within both the innate and adaptive immune systems there is a great deal of redundancy. Thus genetic variation at many loci may influence the penetrance as well as the expressivity of these monogenic disorders. The asymptomatic cases of FI deficiency were detected because their siblings were clinically unwell. Because FI deficiency may be asymptomatic, it is possible that a substantial proportion of cases are undetected. In one report[15] two cases were identified in two non-consanguinous families from the Danish island of Funen. The authors estimate the minimum frequency for the deficient gene to be 0.002 using the Funen island data. However, in two large studies, one in 41 083 Swiss Army recruits,[62] and a second in 145 640 blood donors from Osaka, Japan,[63] no instances of C3 deficiency were identified.

The mainstay of treatment at the present time for these inherited conditions is immunization against pathogens to which affected individuals are particularly susceptible, *Str. pneumoniae*, *H. influenzae* b, *N. meningitidis* (vaccination with polysaccharide antigens types A and C is currently available), together with the administration of prophylactic antibiotics.

An additional potential therapeutic option is replacement of the deficient complement component. Replacement treatment using either fresh-frozen plasma (FFP) or purified protein has been used in C3[37–39,64] and FI deficiencies.[1,9,13,15] In both circumstances, this form of treatment is limited by the high rate of turnover of the deficient protein. Moreover, there are two potential drawbacks: firstly, the replacement of a genetically-absent protein may stimulate an alloimmune response against it; secondly, the reconstitution of the complement system in the acute phase may exacerbate the underlying illness. FFP has been administered in two cases of C3 deficiency and MCGN with no evidence of improvement or deterioration in renal function.[14,39,64] In one of these cases a renal biopsy was performed before and after two months of infusion therapy without evidence of change in renal function, but there was some histological improvement, with a reduction of staining for IgG and C4.[64] The nephritis subsequently showed a definite response to corticosteroid therapy. FFP must still be used cautiously because of the observation that in C3-deficient dogs, the nephritis was worsened by replacement of C3.[56]

The administration of FFP in FI deficiency has resulted in a rapid increase in FB and C3 levels. There was a transient rise in C3d and C4d concentrations, accompanied by a loss of C3 from the patient's red cells together with a slight fall in C4 concentration.[1,9,13,15] No deterioration in clinical condition has been reported in response to FFP administration, although in one case anaphylaxis occurred with the eighth and ninth FFP infusions which were then halted.[15] After an FFP infusion, the decline in the serum concentration of FI is paralleled by that of FB. It has been observed in three instances[4,9,15] that despite the fall in FI and FB levels there is a prolonged effect of FI replacement on the C3 concentration. This starts to decline only after 14 days, at which time there is no antigenically detectable FI, and FB has returned to its baseline level. The mechanism of this discrepancy is unclear. C2 deficiency has been successfully managed with regular FFP replacement therapy, and the clinical improvement, in arthralgia and skin rash for instance, has been observed to last 4–8 weeks, considerably longer than the half-life of C2.[65]

In summary, the four cases of hereditary FI deficiency described in this paper reflect the range of clinical manifestations that can occur in this complement deficiency. The spectrum of illness was from one individual who was completely asymptomatic, to another patient who had recurrent pyogenic infections starting in infancy and continuing until he was diagnosed at the age of 36 years, together with a single episode of a multisystem vasculitic illness. The mechanism by which this variation in disease expression is generated is not known, but it can not be accounted for by any differential affects of FI deficiency on the complement system that can be measured in the laboratory. The clinical consequences of primary C3 deficiency and FH deficiency are similar to those of FI deficiency. There are some differences, however, notably the predisposition towards renal disease in C3 and FH deficiency that has not been found in FI deficiency.

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