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Complement C1q and C8β deficiency in an individual with recurrent bacterial meningitis and adult-onset systemic lupus erythematosus-like illness

SIR, A 49-yr-old nulliparous Caucasoid lady presented with a several week history of florid oral ulceration, malaise, weight loss and fever. There was no rash, photosensitivity, arthralgia, alopoecia, RP, headache, ocular disturbance or recent foreign travel. Past medical history included hypothyroidism associated with anti-thyroid microsomal antibodies for which she was taking thyroxine, bacterial meningitis at the age of 21 and 27 yrs and group A meningococcal septicaemia at the age of 44 yrs. There was a family history of consanguinity. She was dehydrated with low-grade pyrexia of 37.6°C and had multiple oral aphthous ulcers. ESR was >100 mm/h, CRP 11 mg/l (0–10), Hb 9.4 g/l, mean cell volume 92.1 fl, white cell count 5×10^9/l, lymphocytes 1×10^9/l, platelet count 248×10^9/l. Renal function, creatinine phosphokinase and immunoglobulin levels were normal. Liver function tests were abnormal: aspartate transaminase 219 IU/l (0–31), alanine transaminase 117 IU/l (0–31), γGT 331 IU/l (2–30), alkaline phosphatase 177 IU/l (30–130), bilirubin 6 μmol/l (0–17) and albumin 27 g/l (33–47). Hepatitis B surface antigen, hepatitis C antibody, HIV serology were negative and viral studies for CMV, Epstein–Barr virus, Herpes simplex virus and parvovirus did not indicate acute infection. ANAs (1 : 320), anti-Ro antibodies (>100 u/ml, normal range 0–20) and anti-thyroid microsomal antibodies were positive. Anti-double-stranded DNA, aCLs, ANCAs, anti-mitochondrial and anti-liver/kidney microsomal antibodies were negative. Percutaneous liver core biopsy showed mild mononuclear cell infiltrate in the portal tracts, moderate interface hepatitis and focal necrosis and hepatocyte apoptosis within parenchymal areas, features consistent with autoimmune hepatitis.

Whilst C3 and C4 levels were normal, total complement haemolytic activity (CH50) was repeatedly absent indicating possible complement deficiency state. Reconstitution assays were performed in which sera with selective defects of complement components or subunits were mixed with the patient sera and the haemolytic activity of the resultant mixture measured (Table 1). Serum deficient in either the C8β subunit of the C8 protein or the classical pathway component C1q did not restore haemolytic activity to the patient's sera. Normal CH50 was only restored following the addition of both C8 and C1q to the patient's sera. Antigenic assays confirmed complete absence of both C8β and C1q in our patient (Table 1). The genetic basis of the C8β

TABLE 1. Complement Analysis

Classical pathway haemolytic assays:		
Lysis when patient sera added to:		Normal (%)
Buffer alone		<1
Sera depleted in classical pathway components:		
	C1q	4
	C1s	95
	C2	99
	C4	97
Sera depleted in terminal pathway components:		
	C5	97
	C6	98
	C7	100
	C8αγ	99
	C8β	<1
Purified complement components[a]:		
	C8	3
	C1q	2
	C8 and C1q	99
Alternative pathway haemolytic assays:		
Lysis when patient sera added to:		Normal (%)
Buffer alone		<1
Purified complement components[a]:	C8	94

Complement C8 analysis:

	Patient sera	**Pooled human sera**	**C8β-deficient sera**
Total C8 level	7.7 μg/ml	31.6 μg/ml	8.1 μg/ml
C8 western blot	C8β - ABSENT C8αγ - present	C8β and C8αγ - present	C8β - ABSENT C8αγ - present

Genetic basis of C8β deficiency = homozygous R427Term in exon 9 of C8β gene

Complement C1q analysis:

	Patient sera	**Pooled human sera**
C1q levels	0.81 μg/ml	179.1 μg/ml
LMW C1q[b]	PRESENT	Absent

Genetic basis of C1q gene deficiency = homozygous G34R in C1qC gene[c]

[a]The concentration of C8 and C1q added to 2 μl of patient serum in 200 μl diluent was 500 ng; [b]LMW C1q : low molecular weight C1q detected by sucrose gradient ultracentrifugation [3]; [c]Confirmed using *Sfcl* RFLP assay [7]. Amino acid numbering refers to the translational start site (methionine is one), G: glycine; R: arginine; Term: stop codon.

deficiency was a homozygous null mutation within exon 9 of the C8B gene (R427Term, Table 1), a mutation previously identified as the commonest cause of C8β deficiency in Caucasoid individuals [1]. The C1q deficiency was due to a homozygous point mutation (G34R) in the first coding exon of the C1qC gene, a mutation previously identified as a cause of C1q deficiency in German, Indian and Saudi Arabian families [2]. The G34R mutation is associated with the presence of an abnormal, non-functional C1q protein in circulation (low molecular weight C1q) [3] which was detected in our patient (Table 1). Parental DNA was not available and no C1q or C8B mutations were present in a healthy sibling.

A diagnosis of SLE-like illness associated with homozygous C1q deficiency was established together with homozygous C8β deficiency associated with recurrent bacterial meningitis. Immunosuppressive therapy with prednisolone and AZA resulted in complete resolution of her transaminitis. AZA therapy was poorly tolerated, hence maintenance treatment with mycophenolate mofetil was started. Three years later she remains in remission and has not suffered any infective complications.

Homozygous C1q deficiency is a strong susceptibility factor for the development of an SLE-like illness: ~93% of C1q-deficient individuals developed an SLE-like illness, typically beginning in childhood and frequently associated with cutaneous vasculitis, glomerulonephritis and cerebritis [4]. Homozygous deficiency of complement C8 presents with selective deficiency of either C8β or C8α-γ subunits [5] and is associated with an increased risk of recurrent neisserial infections, a feature common to all terminal pathway component deficiencies [6]. To our knowledge, this individual represents the first reported case of combined C1q and C8β deficiency. It was particularly striking that the onset of the SLE-like illness was considerably later than that reported in individuals lacking C1q alone (median onset 6 yrs) [4]. Moreover, her SLE-like illness appeared to be less severe: vasculitis, glomerulonephritis or cerebritis have been described in C1q-deficient individuals with the G34R mutation [3, 7, 8]. Thus, we speculated that the inability to develop terminal pathway-mediated tissue injury (by virtue of the C8β deficiency) could have limited the extent of SLE-induced organ damage in this individual. The scarcity of reports of SLE in individuals with terminal pathway deficiency precluded any attempt to determine if the illness severity in such cases differed from that seen in complement-sufficient SLE patients. However, this unique case supports an important role for the membrane attack complex in the development of tissue injury in SLE.

Rheumatology key message

- Co-existing complement C8 deficiency ameliorated the SLE associated with C1q deficiency.

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Comment on: Infliximab, etanercept and adalimumab for the treatment of ankylosing spondylitis: cost-effectiveness evidence and NICE guidance

Sir, The recent editorial by Wailoo *et al*. [1] on cost-effectiveness evidence of TNF-inhibitors in AS is incorrect and worrying in several respects.

First, the critique of the paper by Kobelt *et al*. [2] is factually wrong. The numbers cited by Wailoo and colleagues are nowhere to be found in this publication, and the 'mistake' is thus a construction. The point they make about the flawed review process, and the implicit critique of the reviewers and editors of *International Journal of Technology Assessment in Health Care* is not substantiated. Instead, there is reason to ask how this editorial cleared this journal's review process.

Second, the authors seem to mix up information that they have gathered through participation in the NICE review process from a manufacturer submission, and what is actually published as a scientific paper. We have no arguments with the procedure that NICE uses qualified reviewers to scrutinize the models and data supplied by the sponsors of the technologies assessed. But the privileged access to information these researchers have should not be used to unfairly criticize and discredit other researchers. It happens now very often that the researchers involved in the NICE process publish their finding as separate scientific papers. This contributes to confusions about what is a NICE application and review, and what is a scientific paper. There are good reasons to keep these two separated, particularly since reviewers can see all models submitted to NICE, but outside researchers have no access to the details of NICE models. This is even more important when the NICE evaluation process has not been completed.

In this case, the manufacturer of infliximab submitted an economic model to NICE and the Assessment Group (AG), along with the necessary raw data (in confidence) to replicate the model. Within this process, the AG found a programming error. The submission stated that patients withdrawing from treatment return to baseline and then progress according to natural history, but the progression was inaccurately programmed in this particular arm of the model. The mistake was corrected and a new version submitted. The authors of the editorial entered this process at a later stage as members of the Decision Support Unit (DSU) commissioned to evaluate the assessment process, and thus use confidential information in an inadequate way.

Third, the editorial rises issues relating to what could be considered conflict of interest and the motivations for the editorial. We understand that the unit at Sheffield University,