Case Report

Familial mesangio-capillary glomerulonephritis with initial presentation as haemolytic uraemic syndrome

Mehrengise Cooper, Mary E. McGraw, D. Joe Unsworth and Peter Mathieson

Southmead Hospital, Bristol, UK

Keywords: complement; C3; C4; familial; Factor H; haemolytic uraemic syndrome

Introduction

Haemolytic uraemic syndrome (HUS) is a clinical syndrome characterized by microangiopathic haemolytic anaemia and thrombocytopenia, often complicated by acute renal failure. Typically, it follows a diarrhoeal illness (d+ HUS), the most well known precipitating organism being the toxin-producing Escherichia coli serotype 0157. Less typical forms of HUS are associated with pregnancy, malignancies, transplant-associated illness and drug regimens including cyclosporin, mitomycin and the oral contraceptive pill. Familial HUS [1] exists in patterns of both autosomal dominant and recessive inheritance. Familial HUS with hypocomplementaemia has been well recognized and an association has been found with abnormalities of Factor H, a factor involved in the alternative pathway of the complement cascade. Recently, the gene for Factor H has been isolated on chromosome 1q32 and mutations of this gene have been seen in families with HUS. We report a family with two generations affected by HUS in whom there were persistently very low levels of C3 but normal C4 suggesting alternative pathway dysregulation, but without demonstrable abnormalities of Factor H. In the first generation, the morphology of the renal lesion over 20 years after the initial presentation was that of membranoproliferative glomerulonephritis (MPGN) type I, suggesting an aetiological relationship between this entity and HUS, with shared mechanisms relating to the alternative pathway of complement, and may be the basis of an autosomal dominant inheritance pattern.

Case

A 1-year-old boy presented initially with diarrhoea having been previously well. Following this episode he became progressively unwell over a 3 week period developing fever, tachypnoea, lethargy and pallor. Clinically, he had features of an upper respiratory tract infection with fluid overload, and systolic blood pressures persisting at 200 mmHg. Initial investigations performed were as follows: haemoglobin (Hb) 5.5 g/dl, platelets 72 × 10⁹, occasional fragmented cells on blood film, sodium 137 mmol/l, potassium 5.0 mmol/l, urea 25.2 mmol/l, creatinine 132 μmol/l. Chest radiograph: mild cardiomegaly; renal tract ultrasound: mild bilateral renal enlargement. He was transfused at this stage and anti-hypertensive therapy was commenced. Autoimmune profile, urinary vanillyl-mandellic acid (VMA) and homovanillic acid (HVA), serum renin and aldosterone levels were normal. Complement assays were C3 0.21 g/l (normal range 0.8–2.1), C4 0.22 g/l (normal range 0.15–0.5).

Initial control of his hypertension was achieved with intravenous labetalol, hydralazine and sodium nitroprusside at maximal dosage. Following the introduction of oral agents, adequate control was gained using several drugs—methyldopa, metoprolol, captopril, nifedipine, frusemide, prazosin and minoxidil. An echocardiogram showed left ventricular hypertrophy; ophthalmology examination was normal. A renal biopsy showed changes consistent with acute HUS. Further analysis of serum complement showed low levels of CH50 (classical haemolytic pathway 50% erythrocyte lysis in vitro) and AP50, indicating alternative pathway dysregulation: CH50 42 (normal range 70–100), AP50 no lysis. Antigenic assays for individual components showed Factor H 384 μg/l (normal range >500), Factor I 48 μg/ml (normal range > 50).

As his blood pressure was controlled, his renal function improved, as did his platelet count. However, on each occasion he has had an intercurrent illness there is evidence of relapse with uraemia and thrombocytopenia. He has not required dialysis
for any episode. He is now 6 years of age and remains on five different anti-hypertensive agents. His serum creatinine is 85–90 μmol/l and his haematology results are normal. He has had a further renal biopsy 4 years following his presentation which is consistent with mesangio-capillary glomerulonephritis. The C3 levels remain persistently low.

**Father’s history**

His father suffered a similar illness in infancy with anaemia and uraemia. During childhood he was noted to have been ‘more pale than usual’ when suffering with intercurrent infections. He had confirmed anaemia, uraemia and thrombocytopenia. At the age of 9 years, a retrospective diagnosis of HUS was made to explain this. During adolescence he developed hypertension, and a renal biopsy was performed at 20 years of age. The changes resembled type I MPGN. Currently, he is hypertensive on treatment with an ACE inhibitor; his creatinine is at the upper end of the normal range. His complement results are C3 0.26 g/l, C4 0.3 g/l, CH50 48, AP50 no lysis, Factor H 526 μg/l, Factor I 39 μg/l. Figure 1 shows the biopsies of father and son.

Like his son, C3 levels persist at a low baseline. The Factor H gene has been sequenced using intronic primers specifically looking at the amplification of each exon of Factor H as described by Richards et al. [2]. No mutations have been found in the family.

**Discussion**

Severe hypertension was the major symptom of concern when the son first presented. This itself could have led to the microangiopathic haemolytic anaemia which was present; however, when he suffered further episodes of haemolysis and thrombocytopenia, he was normotensive, thus making an associated link with hypertension not possible.

Hypocomplementaemia has been described in HUS; in 1973 low levels were first seen in children with HUS and thrombotic thrombocytopenic purpura. One report showed that children who presented with a raised white cell count and a low C3 with D+ HUS had a longer in-patient stay and worse prognosis [3]. Abnormalities of the fast allele component of C3 were also then described in familial and atypical (D−) HUS [4,5], further implicating alternative pathway dysregulation in the pathogenesis of HUS.

C3 levels have been shown to be low even when patients are well, as seen in the case of both father and son in the family described. Like his son, when he suffered the recurrent viral infections encountered in childhood, alternative pathway activation was associated with further episodes of acute HUS. In our family, repeated tests of complement function in both father and son pointed convincingly to an inherited complement defect in the alternative pathway. Normal C4 excluded significant classical pathway activity. Low C3 and undetectable AP50 activity (despite preserved CH50 activity) pinpointed the defect to the alternative pathway.

What is the fate of the kidneys in the long term for those affected by HUS? We know that for those who present with typical D+ HUS the short-term outcome is usually good with full renal recovery. But does this change in the longer term? Twenty-nine patients who had been affected by classical HUS were followed up for 15–28 years. Of these, 21 required peritoneal dialysis, and 25 underwent renal biopsy shortly after recovery: 14 had changes consistent with glomerular thrombotic microangiopathy, and the rest, patchy cortical necrosis. On follow-up, 10 had no renal abnormality, in the rest, 12 had residual renal symptoms (hypertension, proteinuria, mildly reduced GFR), three were in chronic renal failure, and four in end-stage renal failure. Those with more serious outcomes
correlated with the extent of histological damage, although not necessarily with initial clinical severity. Out of 118 children from Argentina who were followed for at least 10 years, 37% were left with sequelae, 3.4% with ESRF.

Several reports of familial HUS have described affected individuals who have developed the disease either in childhood or as adults, typically in early adulthood [6]. The disease process has frequently led to end-stage renal failure necessitating renal transplantation. Recurrences tend to be a major feature suggesting an underlying immune defect—earlier episodes have occasionally been masked and the disease process not recognized. Three male members of one family developed HUS over a 7 year period in early adulthood and all required renal transplantation. Interestingly, there were no abnormalities of complement in this family, but all developed severe disease in adult life, which could have been recurrences of this pathological process. Success of renal transplantation is variable with risk of recurrence in the allograft and transplant failure. In other familial cases of HUS, the long-term effects include hypertension, elevated plasma creatinine [7,8]; children who have a recurrent course have poorer outcomes.

Factor H, the most important regulator of the alternative pathway, is a plasma protein produced by the liver, and acts by accelerating the breakdown of C3bBb, the alternative pathway C3 convertase which is the rate-limiting enzyme of the alternative pathway. It acts as a cofactor for Factor I, which cleaves C3 to the inactive iC3b form [9]. Factor H deficiency has been described in several families with HUS [10], collagen glomerulopathy, and chronic glomerulonephritis. Genetic studies have isolated an area of chromosome 1q which contains the gene encoding Factor H in three families with HUS, with one family a mutation was located at 1q32 [11]. A large Bedouin family was reported as having recessive, atypical relapsing HUS with the gene encoded on chromosome 1q32. In this group, functional analyses showed the Factor H to be structurally normal, with no mutation, and it is expressed and synthesized normally, but not transported properly from the cell [12]. In our family, antigenic levels of Factor H were surprisingly normal. Factor H has many functions and therefore functional moieties; thus, any small mutation could potentially have a detrimental effect on function without affecting the antigenic level of the protein, but this is unlikely in this family given the normally encoded Factor H gene. One group of 13 patients who presented with HUS with normal complement profiles, and normal Factor H levels (with one exception), were found to have clustering mutations in the Factor H gene (HF1) within a region involved with binding C3b; this suggests that the ability of Factor H to protect cellular surfaces is an important path of the pathogenesis of HUS [13].

Factor I also plays an important role in the alternative pathway and abnormalities have been described with meningococcal meningitis [14]. There are no reports of Factor I having been measured in HUS, although theoretically reduced Factor I or functionally abnormal factor could also be involved in the pathogenesis of HUS. In our family, Factor I levels were borderline normal. HUS has not been linked to Factor I abnormalities previously, and the significance of the borderline low levels here is uncertain.

Activation of the alternative pathway has been shown to be associated with familial and recurrent HUS. The C3 levels and Factor H levels are low when patients are disease free. However, when the pathway is challenged, for example, in the presence of an intercurrent infection, as was seen in our family, a cascade of events occurs leading to the clinical, biochemical and haematological picture of HUS.

The fact that the father’s renal biopsy, taken during adult life some 20 years after the initial illness, showed type I MPGN may be instructive. This renal lesion is closely associated with dysregulation of the alternative pathway of complement [15], but why some such patients develop HUS and others develop MPGN remains uncertain. In our family, the father’s condition evolved from clinical manifestations of HUS to a renal biopsy showing MPGN, suggesting shared aetiological mechanisms between these two entities. The end result of this may be the development of either HUS or MPGN; why this occurs is unknown and over time the son’s histological disease may follow his father’s with changes typical of MCGN.

It is important that the association of HUS with abnormalities of the complement pathway are both recognized and further explored in order to extend the understanding of the pathogenesis of the condition. All patients who have developed HUS warrant long-term follow-up—monitoring of blood pressure, proteinuria and GFR—with a close watch in particular of those at high risk, notably infants, familial HUS and those with recurrent disease. There are other complement regulators which may be dysfunctional or deficient in this group of patients, and in the family described Factor H is structurally normal, with no mutation, and it is likely that there is another cause for this persistent alternative pathway activation. Much work has been undertaken into the causes of atypical HUS focusing on complement and alternative pathway activation and Taylor [16] has suggested that future therapeutic moves may include blocking complement pathways.

Acknowledgements. The authors would like to thank Dr David Griffiths, Department of Pathology, Cardiff University for providing the microscopy specimens and Dr Tim Goodship, Schools of Medical Sciences and of Biochemistry and Genetics, University of Newcastle upon Tyne.

Conflict of interest statement. None declared.

References

2. Richards A, Buddles MR, Donne RL et al. Factor H mutations in hemolytic uremic syndrome cluster in exons 18–20, a domain

Received for publication: 7.1.02
Accepted in revised form: 25.7.03