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Exceptional Case

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New combined *CFH/MCP* mutations and a rare clinical course in atypical haemolytic uraemic syndrome

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Abstract

Atypical haemolytic uraemic syndrome (aHUS) is a rare, life-threatening, chronic, genetic disease due to uncontrolled alternative pathway complement activation. In this report, we discuss the case of a heterozygous carrier of a mutation on both factor H and membrane cofactor protein, who persistently presents haemolytic anaemia without need for blood transfusions, normal platelet count, normal renal function and no signs or symptoms of organ injury due to thrombotic microangiopathy 4 years after the diagnosis of aHUS.

Key words: atypical haemolytic uraemic syndrome, membrane cofactor protein, protein factor H

Introduction

Atypical haemolytic uraemic syndrome (aHUS) is a rare, life-threatening, chronic, genetic disease due to uncontrolled alternative pathway complement activation [1]. In most cases, aHUS is associated with mutations or polymorphisms in the genes *CFH* (encoding complement factor H), accounting for 11–29%, *CD46* (MCP, membrane cofactor protein) 3–17% and *CFI* (encoding complement factor I) 2–17% [2]. Mutations in more than one complement gene have been identified in some patients, and nucleotide polymorphisms in *CFH* and *MCP* genes can modulate the risk of aHUS in mutation carriers [3].

Case report

A 31-year-old female presented in our hospital with abdominal pain. The investigations performed showed gallbladder infection and microangiopathic haemolytic anaemia, thrombocytopaenia and acute kidney injury. She had a past medical history of kidney stones and one uneventful pregnancy, and no previous history of diarrhoea. She had no family history of kidney disease or aHUS. Initial investigation revealed the following: haemoglobin 8.3 g/L, platelet count 140×10^6/μL and serum creatinine 3.8 mg/dL. A peripheral blood smear revealed fragmented red cells consistent with thrombotic microangiopathy. The gallbladder infection was treated with broad-spectrum antibiotics with resolution of symptoms. Despite this, after 2 days she became thrombocytopaenic (73×10^6/μL), and serum creatinine rose to 4.8 mg/dL accompanied by haematuria and proteinuria. Plasma exchange (PE) with fresh frozen plasma was promptly started. Her course was complicated with fluid overload and oliguria, leading to the need to perform a brief period of haemodialysis. Following nine sessions of PE over a period of 2 weeks, her parameters improved (haemoglobin 12.4 g/dL, platelet count 220×10^6/μL, lactate dehydrogenase (LDH)

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Table 1. Variations on biochemical parameters during the 4-year follow-up

		Time from hospital discharge					
	Hospital discharge	1 month	6 months	12 months	18 months	3 years	4 years
Serum creatinine (mg/dL)	2.8	1.1	0.7	0.5	0.6	0.5	0.7
Haemoglobin levels (g/dL)	12.0	12.4	11.7	11.2	10.6	11.3	10.4
Platelet count (cells × 10^6/μL)	190	262	253	254	269	195	193
LDH (U/L)	903	1054	774	942	850	972	1554
Serum haptoglobin (g/L)	<10		<10	<10		<10	<10
UPCR (mg/mg)	0.65	0.14	0.07	0.06	0.01	0.08	0.05
Complement C3 (mg/dL)	96.8						77.2
Complement C4 (mg/dL)	21.8						15.7
Homocysteine levels (μmol/L)							10.0

UPCR: protein–creatinine ratio on random urine sample.

1054 U/L, serum creatinine 1.1 mg/dL). The study performed at presentation showed normal ADAMTS13 activity and C3 serum levels. The patient was clinically diagnosed with aHUS, possibly triggered by the gallbladder infection. After 4 years, her renal function and platelet number are normal, but the patient has persistent microangiopathic haemolytic anaemia (Table 1). Despite analytical parameters of haemolysis (LDH 1554 U/L, indirect bilirubin 1.54 mg/dL and absent haptoglobin), the patient has no signs or symptoms of organ injury/thrombosis, no hypertension, no proteinuria and the haemoglobin levels remain stable with no need for blood transfusion. During these 4 years, the patient had possible triggering events (infection and cholecystectomy), with no relapse of aHUS. In keeping with this, we performed a genetic analysis to investigate whether the patient carried some genetic abnormalities associated with aHUS. Mutation screening of *CFH*, *MCP* and *CFI* by Sanger sequencing revealed two heterozygous mutations: a *CFH* (c.3493 C>T, p.His1165Tyr) and an *MCP* (c.1058 C>T, pAla353Val). The first amino acid substitution is not described, and the second is known as a disease mutation [4, 5].

Discussion

aHUS is a challenging disease to manage with a relatively poor prognosis, as up to 65% of patients treated with PE will sustain permanent renal damage, have progression to end-stage renal disease (ESRD) or die within 1 year [6]. In the past years, it became evident that aHUS is associated with mutations in proteins needed for regulation of the alternative complement pathway [7]. Because of the multiple genetic susceptibility factors involving plasma- and membrane-associated regulators, the rarity of combined-mutated patients and the need for a triggering event, it is difficult to predict the clinical course of aHUS. The combined *CFH/MCP* mutations reported in our patient (*CFH* p.His1165Tyr/*MCP* pAla353Val) have not been previously described. As previously reported, it seems that *MCP* or *CFH* mutations confer a predisposition to develop aHUS rather than directly cause the disease, and a second hit is necessary for the full-blown manifestation of the disease, as in all *MCP*-mutated and 70% of *CFH*-mutated patients the onset of aHUS was associated with an infectious event [4]. Our patient showed an impaired capacity to protect vascular endothelial cells from complement attack after the activation caused by the gallbladder infection that led to aHUS presentation. After that, the clinical course was clearly distinct from patients with other *CFH* mutation and was similar to patients with *MCP* mutations described previously. It has been reported that the most severe prognosis is in the *CFH* mutation patients, with 70% reaching ESRD, and that patients with *MCP* mutations have a relapsing course, but none have reached ESRD in the first year [8]. In cases of combined mutations carriers, the concomitant presence of *CFH* and *MCP* risk haplotypes significantly increased disease penetration and modified the prognosis [5]. Among patients with *CFH* mutations, the presence of mutations in other genes did not modify prognosis; however, 50% of patients with combined *MCP* mutation developed ESRD within 3 years from onset compared with 19% of patients with an isolated *MCP* mutation [5]. These two mutations (*CFH* p.His1165Tyr/*MCP* pAla353Val) have a benign phenotype prediction (Polyphen-2), and *MCP* pAla353Val has polymorphic prevalence (1000 Genomes Project). Despite that, their cumulative effect confers a background genetic that seems to be a risk for aHUS; however, their benign character explains the mild clinical course. Indeed, the response to PE would not be expected to be effective for patients with mutations in *MCP*, a transmembrane protein that is not removed by this treatment, but patients with combined mutations achieved remission with PE similar to patients with single non-*MCP* mutations [9]. The excellent response of our patient could be related to the replacement of CFH proteins with PE. In our patient, it seems that the mutated expressed proteins cannot fully protect vascular endothelial cells from activated complement translated by the persistently haemolytic microangiopathic anaemia; however, the regulation of the complement attack is enough to protect her from a relapse.

In summary, we describe the first reported case of aHUS with the combination of a previously described *MCP* mutation with a new *CFH* mutation associated with a rare clinical outcome (persistent haemolysis without renal failure or any other clinical manifestations of endothelial damage or platelet activation). We may therefore speculate that combination of these frequent mutations will worsen the phenotype and could be a common but under-diagnosed phenomenon. The findings in this patient underscore the influence of different genetic abnormalities on disease presentation, response to therapy and outcome in aHUS patients.

Conflict of interest statement

The authors declare that the results presented in this article have not been published previously in whole or part.

(See related article by Sanchez-Niño and Ortiz. Thrombotic microangiopathy: expanding genetic, clinical and therapeutic spectra and the need for worldwide implementation of recent advances. *Clin Kidney J* (2015) 8: 686–689.)

References

1. Hodgkins K, Bobtowskin A, Lane J *et al*. Clinical grand rounds: atypical hemolytic uremic syndrome. *Am J Nephrol* 2012; 35: 394–400
2. Cruzado JM, Rodriguez de Córdoba S, Melilli E *et al*. Successful renal transplantations in a patient with atypical hemolytic uremic syndrome carrying mutations in both factor I and MCP. *Am J Transplant* 2009; 9: 1477–1483
3. Noris M, Remuzzi G. Atypical hemolytic-uremic syndrome. *N Engl J Med* 2009; 361: 1676–1687
4. Caprioli J, Noris M, Brioschi S *et al*. Genetic of HUS: the impact of MCP, CFH, and IF mutations on clinical presentation, response to treatment, and outcome. *Blood* 2006; 108: 1267–1279
5. Bresin E, Rurali E, Caprioli J *et al*. Combined complement gene mutations in atypical hemolytic uremic syndrome influence clinical phenotype. *J Am Soc Nephrol* 2013; 24: 475–486
6. Legendre CM, Licht C, Muus P *et al*. Terminal complement inhibitor eculizumab in atypical hemolytic–uremic syndrome. *N Engl J Med* 2013; 368: 2169–2181
7. De S, Waters A, Segal A *et al*. Severe atypical HUS caused by CFH S1191L—case presentation and review of treatment options. *Pediatr Nephrol* 2010; 25: 97–104
8. Sellier-Leclerc AL, Fremeaux-Bacchi V, Dragon-Durey MA *et al*. Differential impact of complement mutations on clinical characteristics in atypical hemolytic uremic syndrome. *J Am Soc Nephrol* 2007; 18: 2392–2400
9. Kavanagh D, Goodship THJ. Atypical hemolytic uremic syndrome. *Curr Opin Hematol* 2010; 17: 432–438

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