Pediatr Nephrol (2010) 25:97–104
DOI 10.1007/s00467-009-1306-7

BRIEF REPORT

Severe atypical HUS caused by CFH S1191L—case presentation and review of treatment options

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Received: 12 May 2009 / Revised: 10 August 2009 / Accepted: 11 August 2009 / Published online: 24 October 2009

Abstract Atypical hemolytic uremic syndrome (aHUS) has been associated with defective regulation of the alternative complement pathway. Although the use of plasma therapy is recommended, there is little consensus on the optimal treatment regimen. The outcome in many cases remains poor despite an improvement in our understanding of the pathology of aHUS. We have followed a female patient with aHUS associated with heterozygous complement Factor H (CFH) mutation (S1191L) over a period of 15 years. She has been plasma dependent since infancy and has subsequently progressed to end stage kidney disease (ESKD) requiring dialysis treatment. Despite ESKD she still depends on regular plasma infusions to prevent thrombocytopenia. The long-term treatment plan for this patient is challenging. Renal transplantation in patients with the S1191L mutation of the *CFH* gene carries a high risk of failure due to recurrence of aHUS in the renal graft. Thus, the only available curative treatment seems to be combined liver–kidney transplantation, covered by intensive plasma therapy, which comes with a high risk of morbidity and mortality. Antibodies against key activating components of the complement cascade may provide a promising alternative therapeutic strategy in the future. Eculizumab, a monoclonal humanized anti-C5 antibody, has recently been shown to be effective and well-tolerated in patients with paroxysmal nocturnal hemoglobinuria by preventing complement-mediated lysis of affected erythrocytes. Treatment of our patient with eculizumab is supported by recent reports on its successful use in two (pediatric and adult) patients with complement-based aHUS.

Keywords Atypical hemolytic uremic syndrome · Eculizumab · Plasma therapy

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Introduction

Hemolytic uremic syndrome (HUS) is a systemic disease characterized by damage to endothelial cells and erythrocytes, resulting in anemia, thrombocytopenia, microthrombosis and acute renal failure [1, 2]. In children, 90% have the typical or post-diarrheal HUS (D+HUS) caused by the verotoxin-producing/Shiga-like toxin-producing *Escherichia coli*. Of these patients, 75% make a full recovery, with progression to end stage kidney disease (ESKD) as the exception. The remaining 10% have the atypical (aHUS) or diarrhea-negative form (D-HUS), which may be familial or sporadic. Despite an improvement in prognosis following the introduction of plasma therapy, the outcome following diagnosis of aHUS remains poor, with about 10% mortality among patients in the acute phase and an evolution to ESKD in an additional 50% of patients [3, 4].

Over the past decade, aHUS has been demonstrated to be a disorder of the regulation of the factors involved in the alternative pathway of the complement system. Approximately 50% of cases of aHUS are associated with mutations in one or more genes encoding for proteins involved in regulating or activating this pathway, namely complement Factor H (CFH) [5], Factor H-related proteins 1 and 3 (CFHR1 and 3) [6, 7], complement Factor I (CFI) [8, 9], membrane cofactor protein (MCP/CD46) [10, 11] and, more recently, complement Factor B (CFB) (gain of function mutation) [12] and C3 [13]. CFH abnormalities are the most frequent and are found in approximately 30% of all patients with aHUS [3, 4, 14]. Anti-CFH antibodies are present in 10% of childhood cases, with the presence of these antibodies coinciding with the absence of CFHR1 and 3 [15, 16].

Although the use of plasma therapy is recommended [17], there have been no clinical trials, and there is little consensus among treating physicians on its efficacy or the optimal treatment regimen. Fresh frozen plasma (FFP) can be used to replace defective complement factors. Plasmapheresis with FFP removes mutant complement factors, anti-CFH autoantibodies and other triggers of endothelial dysfunction, while simultaneously restoring functional proteins. In addition, plasma exchange prevents the volume overload and hypertension which frequently occurs when large amounts of FFP are infused, especially in patients with compromised renal function [3, 17]. A beneficial effect of plasma therapy in patients with MCP mutations is less likely, as MCP is a membrane-bound regulator of the alternative pathway and not a circulating protein. Published data indicate that 70–80% of patients with these mutations undergo remission from an acute episode, with or without treatment with plasma [18]. Finally, reports suggest that disease recurs in the graft of 50–80% of transplanted aHUS patients, making the rationale for renal transplantation on its own questionable [19, 20].

We have followed a female patient with severe relapsing aHUS associated with a CFH mutation from infancy to adolescence over a period of 15 years. Here, we share our experience and review the clinical challenges and treatment options.

Case report

A 6-month-old Caucasian infant, previously well, presented with lethargy, pallor and hematuria following an upper respiratory tract infection without diarrhea. She was the fourth child of non-consanguineous parents. The pregnancy and neonatal period were uneventful. Her two siblings, her parents and both her paternal and maternal grandparents were healthy with no renal disease. A third sibling was diagnosed with Potter's syndrome of unknown etiology and died soon after birth. Growth and development of our patient were normal prior to presentation.

Initial investigations revealed: hemoglobin 69 g/l, platelet count 141×10^9/l and serum creatinine 75 μmol/l. A peripheral blood smear revealed fragmented red cells consistent with thrombotic microangiopathy (TMA). She subsequently became thrombocytopenic (platelets 74×10^9/l) and her serum creatinine rose to 147 μmol/l. She developed severe hypertension [blood pressure (BP) 140–160/100–120 mmHg] accompanied by proteinuria and oliguria.

Her initial course was complicated by fluid overload and worsening hypertension necessitating a brief period of hemodialysis. She did not respond to plasma infusions, hence plasmapheresis was commenced with FFP as replacement. Following ten sessions of plasmapheresis over a period of 2 weeks, her hematological parameters and creatinine stabilized. A renal biopsy revealed obliterated capillary lumens and fragments of red cells trapped within the matrix, consistent with TMA, in keeping with aHUS. No mutations were detected in the *ADAMTS13* gene, and a genetic work-up of the *CFH* gene was inconclusive.

Plasmapheresis was weaned and replaced by plasma infusions every 2–3 weeks. She subsequently suffered multiple (eight over the course of 7 years) relapses characterized by thrombocytopenia, anemia with mildly elevated lactate dehydrogenase and slightly elevated creatinine which, on most occasions, were triggered by intercurrent upper airway infections. Relapses were typically responsive to intensified (maximum daily) plasmapheresis and/or plasma infusion therapy. Treatment was usually spaced out after stabilization. However, attempts to extend the frequency of plasma infusions beyond 3 weeks resulted in relapses. Intravenous immunoglobulin was unsuccessful. The hypertension and proteinuria of our patient were treated with angiotensin converting enzyme inhibition. At 5 years of age, her renal function remained normal [measured glomerular filtration rate (GFR) 105 ml/min/1.73 m^2].

By 7 years of age, while still on two to three weekly plasma infusions, she had developed progressive renal impairment (serum creatinine 124 μmol/l; GFR 72 ml/min/1.73 m^2). A repeat renal biopsy yielded an insufficient sample, but the results were consistent with a diagnosis of HUS. Her BP control became challenging despite multiple antihypertensives, and she developed left ventricular hypertrophy.

Twelve months later, she developed progressive thrombocytopenia, which prompted a bone marrow biopsy. Her bone marrow was mildly hypocellular but showed normal megakaryocytic precursors. The etiology was therefore presumed to be destruction due to anti-platelet antibodies or antibodies to CFH. In keeping with this hypothesis, she

Table 1 Therapy and outcome in published pediatric aHUS cases with identified mutations

Case	Reference	Age at diagnosis	Mutation	Treatment	Outcome
1	Remuzzi et al. (2002) [35]	1 year	Heterozygous *CFH* mutation: W1183R in SCR20	Combined orthotopic split liver-kidney transplant at age 2 years	Liver failure post-op with irreversible neurological sequelae, requiring liver re-transplantation; death several years later
2	Richards et al. (2003) [11]	8 years (sibling of case 3)	Heterozygous *MCP* mutation: T822C (S206P)	Supportive only	Recovery
3	Richards et al. (2003) [11]	15 years (sibling of case 2)	Heterozygous *MCP* mutation: T822C (S206P)	Plasma infusion/exchange	Recovery
4	Richards et al. (2003) [11]	9 years (sibling of case 5)	Homozygous *MCP* mutation: T822C (S206P)	Plasma exchange	One relapse with spontaneous recovery
5	Richards et al. (2003) [11]	17 years (sibling of case 4)	Homozygous *MCP* mutation: T822C (S206P)	Plasma infusion	Recovery
6	Cheong et al. (2004) [36]	3 months	Compound heterozygous *CFH* mutation: V62I (exon 2) and C926F (exon 17) in SCR15	Auxiliary partial orthotopic liver transplant at age 30 months	Death 11 months post-TX due to infections and PTLD
7	Dragon-Durey et al. (2004) [37]	11 months (first cousin of case 18)	Homozygous *CFH* mutation: Y899Stop in SCR15	Renal transplant at age 7 years with plasma infusion ×2 years post-TX	Recovery
8	Dragon-Durey et al. (2004) [4]	6 months	Heterozygous *CFH* mutation: Q924Stop in SCR15	Renal transplant age 6 years	Well at 10 year follow-up
9	Dragon-Durey et al. (2004) [37]	16 months	Heterozygous *CFH* mutation: N774Stop in SCR13	Renal transplant age 4 years	Well at 4 year follow-up
10	Dragon-Durey et al. (2004) [4]	18 months	Heterozygous *CFH* mutation: I136Stop in SCR2	Plasma infusions	Death at age ~ 2 years
11	Dragon-Durey et al. (2004) [37]	9 months	Heterozygous *CFH* mutation: C915S in SCR15	Renal transplant age 5 years	aHUS relapse requiring transplantectomy and chronic hemodialysis
12	Filler et al. (2004) [38]	1 year	Heterozygous *CFH* mutation: Insertion of 12 amino acids in SCR20	Plasma infusion/exchange	Recovery
13	Olie et al. (2004) [24]	3 years (elder sister of cases 22 & 23)	Heterozygous *CFH* mutation: S1191L in SCR 20	Renal transplant at age 6 years	Transplant failure x2 secondary to aHUS recurrence
14	Dragon-Durey et al. (2005) [39]	10 years	CFH autoantibodies	Plasma infusion; IVIg	End-stage renal failure after 2 months requiring bilateral nephrectomy
15	Dragon-Durey et al. (2005) [39]	3 years	CFH autoantibodies	Plasma infusion/exchange; azathioprine	4 recurrences in 17 months
16	Dragon-Durey et al. (2005) [39]	9 years	CFH autoantibodies	Plasma infusion/exchange; steroids	3 recurrences in 3 months

Table 1 (continued)

Case	Reference	Age at diagnosis	Mutation	Treatment	Outcome
17	Licht et al. (2005) [40]	8 months	Homozygous *CFH* mutation: Y899Stop in SCR15	Plasma infusion	Well on prophylactic plasma therapy x18 months
18	Nathanson et al. (2001, 2006) [41, 42]	5 months (first cousin of case 7)	Homozygous *CFH* mutation: Y899Stop in SCR15	Plasma infusion/exchange	Bilateral nephrectomy after 4 years of plasma therapy due to uncontrolled hypertension
19	Remuzzi et al. (2005) [43]	13 months	Heterozygous *CFH* mutation: E1172Stop in SCR20	Combined liver-kidney transplant	Primary liver non-function post-TX; death post-TX day 3
20	Saland et al. (2006) [44]	4 months	Compound heterozygous *CFH* mutations: C973Y in SCR16 and V1197A in SCR20	Living-related renal transplant, with transplant failure secondary to recurrent aHUS resulting in combined liver-kidney transplant (with pre- and peri-TX plasma therapy, as well as post-TX anticoagulation)	Well at age 8.5 years; chronic bronchiectasis
21	Cho et al. (2007) [45]	22 days	Compound heterozygous *CFH* mutations: C1077W in SCR18 and Q1139Stop in SCR19	Plasma infusion	Recovery; well at 20 months
22	Davin et al. (2006, 2008) [26, 46]	5 years (monozygotic twin of case 23)	Heterozygous *CFH* mutation: S1191L in SCR20	Renal transplant	Well 5 years post-transplant; two aHUS relapses triggered by primary CMV infection and reactivation
23	Davin et al. (2006, 2008) [26, 46]	5 years (monozygotic twin of case 22)	Heterozygous *CFH* mutation: S1191L in SCR20	Plasma exchange	aHUS relapse x3 with infections
24	Jalanko et al. (2008) [47]	1 year (niece of case 25)	Heterozygous *CFH* mutation: R1215Q in SCR20	Combined liver-kidney transplant, with pre- and peri-TX plasma therapy, as well as post-TX anticoagulation	Well 15 months post-TX
25	Jalanko et al. (2008) [47]	16 years (aunt of case 24)	Heterozygous *CFH* mutation: R1215Q in SCR20	Combined liver-kidney transplant, with pre- and peri-TX plasma therapy, as well as post-TX anticoagulation	Well 8 months post-TX
26	Saland et al. (2009) [48]	9 months	Heterozygous *CFH* mutation: S1191L in SCR20	Combined liver-kidney transplant, with pre- and peri-TX plasma therapy, as well as post-TX anticoagulation	Well 21 months post-TX
27	Sethi et al. (2009) [49]	7 months	Homozygous *CFH* mutation: Deletion of four nucleotides (c.3693-3696ATAG) in exon 23, inducing a frameshift in the coding sequence, abolishing the normal stop codon	Supportive therapy only	Chronic kidney disease, on dialysis
28	Watt et al. (2009) [50]	1 year	Heterozygous *MCP* mutation: IVS2 + 2 T → G (intron 2) - splice site mutation	IVIg; steroids	Steroids at onset of febrile illness, without recurrence of aHUS

CFH, Complement factor H; MCP, membrane cofactor protein; PTLD, post-transplant lymphoproliferative disease; SCR, short consensus repeats; IVIg, intravenous immunoglobulin; CCP, complement-control proteins; aHUS, atypical hemolytic uremic syndrome; CMV, cytomegalovirus; TX, treatment

responded to high-dose prednisone. Severe hypertension with BP levels of 135/80 mmHg on five different antihypertensives and thrombocytopenia prompted another hospital admission a few months later, and her platelet count recovered following administration of intravenous immunoglobulin. Despite all treatment efforts, this patient developed ESKD (GFR 20 ml/min/1.73 m^2) and after several months of hemodialysis, peritoneal dialysis (PD) was commenced. At the present time, she still requires plasma infusions at 2-week intervals to control the

Table 2 Treatment options in aHUS with *CFH* mutations

Treatment	Implications
Plasma therapy (plasma-infusion/-pheresis)	Invasive therapy; protein and volume challenge; sensitization risk; infection risk
Kidney transplantation	High risk of graft loss despite intensive plasma therapy
Combined liver and kidney transplantation	Successful in combination with intensive peri-transplant plasma therapy; however, carries still high morbidity and mortality risk
CFH concentrate	Under development - not available yet
Monoclonal anti-C5 antibody	Effective in PNH; successful use reported in two aHUS patients

PNH, paroxysmal nocturnal hemoglobinuria

hematological component of her aHUS, mainly thrombocytopenia, and she remains on PD. Despite treatment with darbepoetin and iron, her hemoglobin and absolute reticulocyte counts run slightly low, ranging from 100 to 115 g/l and from 30 to 50×10^9/l, respectively.

During her terminal crisis she responded to steroids and intravenous immunoglobulin, although anti-platelet antibodies as well as anti-CFH autoantibodies were repeatedly negative. However, repeat genetic screening of the *CFH* gene has revealed a heterozygous mutation in exon 22 of CFH resulting in the exchange of a serine by leucine at position 1191 (S1191L). The same mutation was also found in the patient's mother, who is healthy. CFHR1 and 3 were present, and no additional mutations were found in the genes encoding CFI, CFB or MCP.

Discussion

During the last few years it has become evident that aHUS is strongly associated with mutations in the proteins needed either for activation or regulation of the alternative complement pathway. In addition to CFI, CFB, MCP and C3, CFH and other members of the family of proteins structurally and functionally related to CFH, especially isoforms 1 and 3 of CFHR, are involved in aHUS pathology; their pathogenetic relevance, however, remains controversial, as evidenced by discussions in the literature [6, 7, 21].

CFH mutations are categorized into two groups. The first type of mutation affects the CFH plasma level, while the second type impairs protein function. To date, over 100 distinct CFH mutations have been reported in aHUS patients. Nearly all of these are heterozygous, with only a few homozygous mutations with complete CFH deficiency reported [3]. The majority of mutations are localized to short consensus repeat (SCR) units 19 and 20, the carboxy-terminal recognition domain of CFH protein [14]. These mutations cause either truncations or amino acid substitutions (missense mutations), resulting in CFH malfunction [22, 23]. The carriers of such mutations express CFH molecules that present normal complement regulatory activity in plasma but lack the capacity to protect vascular endothelial cells from complement attack. Hence, any trigger of complement activation—for example, infectious diseases—results in tissue damage, further entertaining complement activation as well as inducing the coagulation cascade with clot formation and thromboembolic end organ damage [2].

In addition to *CFH* mutations, CFH autoantibodies also lead to an acquired defect in CFH function. The binding epitopes of the autoantibodies have been recently localized to the C-terminal recognition domain of CFH, which results in a functional equivalent to a C-terminal CFH mutation [16]. While CFH autoantibodies are not linked to mutations in the *CFH* gene, the absence of CFHR1 and 3 has recently been associated with the presence of CFH autoantibodies (*DEAP*-HUS: deficient for CFHR proteins and CFH autoantibody-positive) [15].

With only a few cases documented in the literature, efforts to establish a treatment consensus for aHUS in children have only recently been undertaken [17]. As a result, pediatric aHUS patients with known mutations were often treated based on the experience of their physicians and institutions, with widely varying success rates. Table 1 summarizes the treatment experiences of the 28 pediatric cases of aHUS that have been published to date.

Six cases with the *CFH* mutation S1191L have been reported in the literature, with the first three cases belonging to the same family: the eldest daughter and the identical twin sisters. The eldest daughter and one of the identical twin sisters had recurrence of aHUS post-transplant [24–26]. The fourth reported case is a 7-month-old female infant who presented with aHUS associated with combined de novo CFH mutations (S1191L and V1197A); her recurrences have so far been successfully treated with plasma infusions, but the long-term tolerance and efficacy of this therapy is unknown [27]. The other two cases are a mother and her daughter. The affected mother died, and the outcome of the daughter has not yet been reported [28]. Therefore, it is fair to conclude that the outlook for this mutation is discouraging.

Given this background, treatment of our patient is challenging. Despite the development of ESKD, she continues to be plasma dependent to maintain the stability of her hematological parameters, which is unusual.

Based on the available literature, our management options are the following:

- Renal transplantation: In patients with *CFH* mutations there is a 30–100% risk of graft loss due to aHUS recurrence or graft thrombosis. Kidney transplantation under pre-, intra- and post-operative intensive plasma therapy is not successful in all patients [20].
- Combined liver and kidney transplantation: As CFH is synthesized in the liver, liver transplantation has been proposed for patients with severe forms of aHUS and *CFH* mutations. Combined liver and kidney transplantation under pre- and intra-operative plasma therapy and post-operative anticoagulation has been successful in a small number of patients with *CFH* mutations. However, careful evaluation of the potential risks and benefits is needed [29].
- CFH concentrate infusions: A human plasma-derived CFH concentrate is being developed by the Laboratoire Français du Fractionnement et des Biotechnologies. However, this compound is not yet available [3].
- Antibodies: Antibodies against key activating components of the complement cascade, such as the humanized monoclonal anti-C5 antibody eculizumab, may be beneficial. Complement inhibition at this stage decreases damage mediated by the generation of the anaphylotoxin C5a and the formation of the membrane attack complex (MAC), C5b-9 on cell surfaces, while it preserves early complement components that are critical for the clearance of microorganisms and immune complexes. The terminal complement inhibitor eculizumab has been recently shown to be effective and well tolerated in patients with paroxysmal nocturnal hemoglobinuria (PNH), another alternative complement pathway-mediated disorder affecting erythrocytes [30–32]. Treatment of our patient with eculizumab is supported by its successful use in an 18-month-old boy with congenital aHUS following his fourth relapse, which was resistant to plasmapheresis, and a 37-year-old female with aHUS recurrence after her second renal transplantation [33, 34].

The implications of the various treatment options are given in Table 2.

In conclusion, despite major progress in our understanding of the underlying pathogenetic mechanisms, aHUS remains a severe childhood disease with potential adverse outcomes, including the development of ESKD, disease recurrence after transplantation and death. Identification of the key role of dysregulation of the alternative complement pathway in the pathogenesis of aHUS allows for the development of targeted treatment strategies exceeding plasma transfusion in efficacy. Future treatments may include the use of purified complement regulatory proteins to restore missing function, or targeted interruption of the overactive complement cascade by the use of specific antibodies or affinity directed complement regulators. Finally, autoantibody-mediated aHUS (*DEAP*-HUS) may favorably respond to plasmapheresis or immunosuppressants. Neither of these approaches has been proven in controlled prospective treatment trials, and collaborative efforts seem inevitable given the small number of patients.

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