ABSTRACT

Atypical haemolytic uraemic syndrome is caused by alternative complement pathway dysregulation. It has recently been recognised that most cases are due to genetic factors and a growing list of mutations has been described. Atypical haemolytic uraemic syndrome is associated with a dismal prognosis, a relapsing course, high acute mortality and frequent progression to end-stage renal disease.

We describe a five-year-old boy admitted with a first recurrence of atypical haemolytic uraemic syndrome. The primary onset of the disease was at 15 months of age, following which there was complete recovery of haematological and renal parameters. His family history was significant in that his mother had died at the age of only 23 years of a stroke with associated thrombotic microangiopathy, suggesting a familial form of the disease. Sequencing of the gene encoding complement factor H revealed a heterozygous SCR20 mutation (3644G>T, Arg1215Leu), confirming the diagnosis. The patient was successfully treated with fresh frozen plasma infusions that induced disease remission.

We also review currently evolving concepts about atypical haemolytic uraemic syndrome caused by factor H mutation, its diagnosis, the role of genetic testing and management strategies in children.

Key-Worlds: Atypical haemolytic-uraemic syndrome; children; complement; factor H.

INTRODUCTION

Haemolytic uraemic syndrome (HUS) is part of a group of thrombotic microangiopathies affecting multiple organ systems, but predominantly the kidney. It is defined by a clinical triad of microangiopathic haemolytic anaemia, thrombocytopenia and acute renal injury, induced by the formation of platelet thrombi in the microcirculation of the kidney. Although rare, it is the most common cause of acute renal failure in young children.

HUS is classically divided into typical or atypical (aHUS) subtypes, based on clinical presentation and the association with bacteria that produce shiga-like toxin (Stx), frequently *Escherichia coli* of the O157:H7 serotype. Typical (or Stx associated) HUS is the most common form in children, accounting for 90% of all cases. It usually occurs after a prodromal episode of
bloody diarrhoea (D+), has a self-limiting course and relatively good prognosis, with complete recovery of renal function.

On the other hand, atypical HUS (the non-Stx related form) can occur from infancy to adulthood, is responsible for only 10% of cases in children and is not associated with a diarrhoeal prodrome (D-). Although the clinical presentation of aHUS can be variable, it usually carries a poor prognosis, with a relapsing course, high acute mortality (25%), frequent progression to end-stage renal disease (ESRD) (50%) and recurrence of the syndrome after kidney transplant (30-100%)\(^1\text{-}^5\).

It is now recognised that up to 60% of aHUS is associated with mutations in genes encoding alternative complement pathway components and their regulators, leading to excessive complement activation and consequent endothelial damage. Some genetic mutations have been identified including: i) ‘loss of function’ mutations in genes encoding complement regulatory proteins which normally protect host cells from complement activation [factor H (CFH), factor I (CFI); complement factor H-related proteins (CFHR) and membrane cofactor protein (MCP or CD46)], ii) ‘gain of function’ mutations in the genes encoding the complement activators [complement factor B (CFB) and C3], iii) mutations in thrombomodulin (THBD), and iv) functional factor H deficiency due to anti-CFH auto antibodies\(^6\).

The latest advances in understanding the pathogenesis of aHUS have led to a revised classification of the syndrome. As a result, according to Noris M. et al.\(^6\), aHUS can be categorised as genetic, acquired or idiopathic. Genetic aHUS can also be classified as multiplex (i.e. familial with two or more affected family members) or simplex (i.e. a single occurrence in a family)\(^6\). Familial aHUS occurs in less than 20% of cases and has poor prognosis, with a rate of either ESRD or death of 50 to 80%. Both autosomal dominant and recessive patterns of inheritance have been reported\(^7\).

In this article we report a rare paediatric case of genetic, familial aHUS, caused by factor H mutation, with a recurrent clinical course. Currently evolving concepts about aHUS will be discussed, with a special focus on diagnostic strategies, the role of genetic testing and new management strategies for children with aHUS.

### CASE REPORT

A five-year-old boy was admitted to our paediatric nephrology unit with the diagnosis of a first recurrence of aHUS. Disease onset was at 15 months of age, when he had been admitted with a two-week history of weakness, pallor, loss of appetite, and lethargy. At that time, there was no history of fever, diarrhoea, vomiting, respiratory or urinary symptoms and no other signs of disease were noted. There was no exposure to sick contacts. He had no previous serious illnesses, took no medications, and had received all immunisations. His parents were not consanguineous, but his family history was significant in that his mother had died at the age of only 23 years of a stroke and thrombotic microangiopathy. Physical examination revealed no significant abnormality, except pallor. Laboratory evaluation demonstrated anaemia [haemoglobin (Hgb) 5.6 g/dL], normal white blood cell count (WBC) (8.6x10\(^3\)cells/dL), mild thrombocytopenia (125x10\(^9\)/L), elevated reticulocyte count (20%) and high lactate dehydrogenase (LDH) (4354 IU/L; normal range: 230-460). Direct Coombs test was negative. A peripheral blood film showed fragmented red blood cells (RBC), polychromasia, and acanthocytes, consistent with the diagnosis of microangiopathic haemolytic anaemia. Investigations also revealed mild renal injury [elevated blood urea nitrogen (BUN) 9.6 mmol/L; serum creatinine (Scr) 40\(\mu\)mol/L; urinalysis with mild haematuria (10-15 RBCs/FPF) and protein/creatinine ratio 1.1 mg/mg].

A presumptive diagnosis of aHUS was made, with the suspicion of a familial disease. The patient was managed with fluid and electrolyte therapy and there was complete resolution of the haematological and renal abnormalities. Anaemia was well tolerated and no blood transfusion was necessary during this first episode.

Studies of Von Willebrand factor-cleaving protease activity (ADAMTS 13), including genetic analysis, were normal. Over the following four years he was well and developed normally.

At the age of five years, the child was readmitted with a 1-week history of jaundice, fatigue, pallor, lethargy and intermittent abdominal pain. Once again, there was no history of preceding diarrhoea, fever or vomiting, though he did have an upper respiratory tract infection treated with a course of amoxicillin
and clavulanate two weeks prior to admission. On physical examination, the child had normal vital signs except for high blood pressure (135/89 mmHg). Inspection revealed pallor, mild icterus and multiple scattered petechiae. He had no other rashes and no lymphadenopathy, abdominal tenderness or hepatosplenomegaly. Neurological examination was normal. Laboratory findings were Hgb 6.7g/dL; WBC 5.4x10^3 cells/dL and platelet count 48x10^9/L. The peripheral blood smear showed fragmented erythrocytes, schizocytes, marked anisocytosis and thrombocytopenia. Serum biochemistry was urea 7.9 mmol/L; Cr 129.9 μmol/L; LDH 3522 IU/L; haptoglobin <0.243 g/L (0.45-2.05); and normal electrolytes. Urinalysis revealed microscopic haematuria (15 RBCs/HPF) and proteinuria (protein/creatinine ratio 2.3mg/mg). D-dimer and direct Coombs tests were negative. The coagulation screen (including prothrombin time, activated partial thromboplastin time, fibrinogen, and antithrombin III levels) was normal.

This second presentation with microangiopathic haemolytic anaemia, thrombocytopenia and acute renal injury, and on this occasion, with associated hypertension, was consistent with a first recurrence of aHUS. He was managed conservatively with fluid and electrolyte monitoring, blood transfusion, blood pressure control and nutritional advice. Fresh frozen plasma (FFP) infusion was started (10 ml/kg twice daily for the first two weeks, reduced to once a day in the third week). Blood pressure control was achieved with triple antihypertensive medication (nifedipine 20mg bid, enalapril 10mg bid, losartan 25mg id). Dialysis was not required. The subsequent course was favourable and after 3 weeks the child was discharged with improved haematologic and renal parameters (Hgb 8.4 g/dl; platelets 229x10^9/L; Cr 44.2 μmol/L and urea 24.5mmol/L).

An extensive work-up was performed. Anti-nuclear antibodies, anti-double stranded DNA antibodies, anti-neutrophil cytoplasmic antibody, antibodies to extractable nuclear antigens and glomerular basement membrane were all negative. Serum levels of immunoglobulins (G, M, A), were normal. Complement C3 was normal (154.0 mg/dL) and C4 level low (8.1mg/dL, 83-177). Studies of ADAMTS 13, including functional and genetic analysis, were again normal. Serum factor H and factor I levels were in the normal range. Genetic studies performed at Mario Negri Institute for Pharmacological Research (Bergamo, Italy), under the auspices of the International Registry of Recurrent and Familial HUS/TTP, disclosed a heterozygous mutation in factor H gene, leading to the amino acid substitution (Arg1210Leu) at position 3644 (3644G>T) in short consensus report unit 20 (SCR20) hot-spot mutation region of the terminal part of the CHF molecule. Investigation of other genetic disorders of complement regulation performed at the same institution (CD46-MCP, factor I and ADAMTS 13) were all negative.

DISCUSSION

Atypical HUS is a rare disease and remains a diagnostic and therapeutic challenge. A high index of suspicion is required for early recognition and appropriate treatment. Children with aHUS have a varied clinical presentation and course. These are influenced by the underlying gene mutation, which is also significant in predicting response to treatment and outcome.

Our patient had an initial presumptive diagnosis of aHUS based on clinical presentation, laboratory findings and familial background. Sequencing of the gene CFH encoding complement factor H revealed a heterozygous SCR20 mutation [(3644G>T, resulting in the exchange of arginine by leucine at position 1215 (Arg1215Leu)] that confirmed the diagnosis. Mutations at the same position of CFH sequence have already been described in other patients affected by aHUS and the presence of a SCR20 mutation of factor H is a strong predisposing factor for the disease.

Mutations in gene encoding for factor H are the most common cause of aHUS (30%). Patients are generally heterozygous and the disease presents...
early in childhood in approximately 70% of affected individuals. Children with aHUS caused by CFH gene mutation usually have the worst prognosis with about three quarters developing ESRD or dying following the presenting episode or as a consequence of relapse. In addition, the rates of relapse and post transplant recurrence are high9-13. Moreover, our patient’s family background with the early death of the affected parent makes us concerned that there may be an adverse future clinical course. Consequently, determination of the best therapeutic strategy is challenging.

Plasma therapy, including plasma infusion (PI) or plasma exchange (PEX), is considered the first-line therapy for aHUS and the recommended approach for its treatment in the treatment of children with aHUS due to complement dysregulation17-19. Because it is known that CFH is synthesised by the liver, combined liver-kidney transplantation could also be an option but there are currently insufficient data to recommend this practice20.

In conclusion, this case report highlights the most recent advances in aHUS in children, in particular the advantage of genetic diagnosis. Prognosis is usually poor and careful long-term follow-up is required. Novel treatment options are now under development which may improve patient outcomes.

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Conflict of interest statement. None declared.

References
Atypical haemolytic-uraemic syndrome caused by factor H mutation: case report and new management strategies in children


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