

Anti-Factor H Antibody–Associated and Complement–Mediated Atypical Hemolytic Uremic Syndrome With Homozygous Cfhr1-Cfhr3 Deletion: A Case Report

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Case Report

Keywords: Atypical hemolytic uremic syndrome, Anti factor H antibody, CFHR1 and CFHR3 gene, complement mediated thrombotic angiopathy, plasma exchange

Posted Date: October 20th, 2026

DOI: <https://doi.org/10.21203/rs.3.rs-10202993/v1>

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Additional Declarations: No competing interests reported.

Abstract

Background

Atypical uremic syndrome is rare, life-threatening complement mediated thrombotic microangiopathy characterized by microangiopathic hemolytic anemia, thrombocytopenia and acute kidney injury. Anti complement factor H (CFH) antibody associated atypical HUS is strongly associated with homozygous deletion of the CFHR1 and CFHR3 genes. Early diagnosis and prompt treatment are essential to prevent irreversible renal injury.

We Report a case of previously healthy 10-year-old girl presented with fever, upper respiratory tract symptoms, vomiting, severe anemia, thrombocytopenia, hypertension, acute kidney injury without preceding diarrheal illness. Laboratory investigations demonstrated microangiopathic hemolytic anemia, with schistocytes, elevated lactate dehydrogenase, thrombocytopenia, proteinuria and renal dysfunction. Complement levels C3, C4 within normal limits. Antifactor H antibody titre was markedly elevated (18224 U/ml). Whole -exome sequencing with copy number variation analysis revealed a homozygous deletion involving the CFHR1 and CFHR3 genes. The patient underwent five sessions of therapeutic plasma exchange along with corticosteroids and supportive care, resulting in normalization of platelet count, improvement in renal function and clinical recovery.

Conclusion

This case highlights the importance of combining the clinical findings with complement studies and genetic analysis in diagnosing complement mediated thrombotic microangiopathy. Early plasma exchange resulted in favorable renal recovery in this child with anti-factor H antibody associated aHUS.

Categories : General medicine, Pediatrics, Hematology.

Background

Atypical haemolytic uremic syndrome (aHUS) is a rare, life-threatening form of thrombotic microangiopathy (TMA) characterised by the triad of microangiopathic haemolytic anaemia, thrombocytopenia and acute kidney injury. Unlike Shiga toxin-producing haemolytic uremic syndrome, aHUS results from dysregulation of the alternative complement pathway, leading to uncontrolled complement activation, endothelial injury, platelet activation and widespread microvascular thrombosis. The estimated annual incidence of aHUS is approximately 0.5–2 cases per million population, with children accounting for a substantial proportion of affected individuals. Contemporary genetic studies have expanded understanding of complement dysregulation in aHUS (15).

Among the various causes of complement-mediated aHUS, anti-factor H antibody-associated disease represents a distinct acquired subtype, accounting for approximately 5–25% of paediatric cases depending on the geographic population studied. Anti factor H is the principal regulator of the alternative complement pathway, and circulating autoantibodies against factor H impair its regulatory function,

resulting in persistent complement activation and endothelial damage. Although serum C3 levels are frequently reduced, normal complement levels do not exclude the diagnosis.

Anti-factor H antibody-associated aHUS shows a strong genetic association with homozygous deletion of the *CFHR1* and *CFHR3* genes. These deletions are thought to impair immune tolerance to complement factor H, predisposing susceptible individuals to the development of pathogenic autoantibodies. Therefore, the diagnosis requires integration of clinical findings with complement studies, anti-factor H antibody measurement and genetic analysis. Early recognition is crucial because delayed diagnosis may lead to irreversible kidney injury, chronic kidney disease or death.

The management of anti-factor H antibody-associated aHUS has evolved considerably over the past decade. Therapeutic plasma exchange remains an effective treatment by removing

circulating anti-factor H antibodies and replacing functional complement factor H. Immunosuppressive therapy is commonly administered to reduce antibody production and minimise the risk of relapse. Although complement inhibitors such as eculizumab have significantly improved outcomes, their limited availability and high cost continue to restrict their use in many low- and middle-income countries.

We report the case of a previously healthy 10-year-old girl with anti-factor H antibody-associated aHUS presenting with severe thrombotic microangiopathy, markedly elevated anti-factor H antibody titre (18,224 U/mL) and genetically confirmed homozygous *CFHR1*–*CFHR3* deletion. Early diagnosis and prompt treatment with therapeutic plasma exchange and corticosteroids resulted in complete haematological recovery and restoration of renal function. This case highlights the importance of recognising this rare but treatable subtype of aHUS and emphasises the role of genetic evaluation in confirming the diagnosis and guiding management. Detailed evaluation of complement genetic variants may further refine diagnosis and risk stratification (20).

Case presentation

A previously healthy 10-year-old girl presented with a 5-day history of fever, upper respiratory tract symptoms, vomiting and reduced urine output. There was no preceding diarrhoeal illness, recent travel, exposure to sick contacts or history of ingestion of undercooked food. She had no significant past medical history, was not receiving any regular medications and had no previous episodes of similar illness. Her developmental milestones were appropriate for age, and there was no family history of renal disease, thrombotic microangiopathy or autoimmune disorders.

On admission, she appeared ill and markedly pale. Her blood pressure was elevated for age, while the remaining vital signs were stable. Systemic examination revealed no skin rash, purpura or active bleeding. There were no focal neurological deficits. Cardiovascular, respiratory and abdominal examinations were otherwise unremarkable, with no hepatosplenomegaly or peripheral oedema.

In view of the combination of severe anaemia, thrombocytopenia, hypertension and acute kidney injury, a thrombotic microangiopathy was suspected. She was admitted for further evaluation, supportive management and definitive diagnostic work-up.

Investigations

Initial laboratory investigations demonstrated severe microangiopathic haemolytic anaemia, thrombocytopenia and acute kidney injury. The haemoglobin level was **5.2 g/dL**, platelet count was **58 × 10⁹/L**, and peak serum creatinine was **2.0 mg/dL**. The reticulocyte count was **5%**, and peripheral blood smear demonstrated numerous **schistocytes**, consistent with microangiopathic haemolytic anaemia. Serum lactate dehydrogenase (LDH) was elevated at **691 U/L**. Total bilirubin was **2.3 mg/dL** with a direct bilirubin of **0.9 mg/dL**, supporting ongoing haemolysis. The direct antiglobulin (Coombs) test was **negative**, excluding immune-mediated haemolysis.

Urinalysis revealed **3 + proteinuria** on dipstick examination, consistent with renal involvement. Serum complement levels (**C3 and C4**) were within normal limits. Antinuclear antibody (ANA) testing was **negative**, making an underlying autoimmune disorder less likely. Stool testing for **Shiga toxin-producing organisms** was **negative**, thereby excluding typical (infection-associated) haemolytic uraemic syndrome.

Although ADAMTS13 activity was not performed (unavailability in our centre), the overall clinical presentation, including the absence of neurological manifestations, together with the subsequent immunological and genetic findings, favoured complement-mediated atypical haemolytic uraemic syndrome over thrombotic thrombocytopenic purpura. The broader spectrum of thrombotic microangiopathies and their differential diagnosis has been well described in previous reviews (12).

Further evaluation demonstrated a markedly elevated **anti-factor H antibody titre of 18,224 U/mL**. Whole-exome sequencing with copy number variation analysis identified a **homozygous deletion involving the CFHR1 and CFHR3 genes**, confirming the diagnosis of **anti-factor H antibody-associated complement-mediated atypical haemolytic uraemic syndrome**.

Differential diagnosis

The differential diagnosis included **Shiga toxin-producing haemolytic uraemic syndrome (STEC-HUS)**, **thrombotic thrombocytopenic purpura (TTP)**, **disseminated intravascular coagulation (DIC)** and **secondary thrombotic microangiopathy** associated with autoimmune disorders.

Typical HUS was considered unlikely because there was **no preceding diarrhoeal illness**, and stool testing for **Shiga toxin-producing organisms was negative**. TTP was also considered; however, the patient had **predominant acute kidney injury, no neurological manifestations**, and **markedly elevated anti-factor H antibody titres** with subsequent identification of a **homozygous CFHR1–CFHR3 deletion**, supporting complement-mediated aHUS. Although ADAMTS13 activity could not be assessed because

the test was unavailable at our institution, the overall clinical, immunological and genetic findings favoured a diagnosis of aHUS.

Autoimmune-associated thrombotic microangiopathy was considered less likely because **ANA testing was negative**, and there were no clinical features suggestive of systemic autoimmune disease. Disseminated intravascular coagulation was excluded based on the absence of clinical evidence of sepsis or consumptive coagulopathy together with the characteristic features of thrombotic microangiopathy.

Based on the constellation of **microangiopathic haemolytic anaemia, thrombocytopenia, acute kidney injury, markedly elevated anti-factor H antibody titre, and homozygous CFHR1–CFHR3 deletion**, a final diagnosis of **anti-factor H antibody-associated complement-mediated atypical haemolytic uraemic syndrome** was established.

Treatment

Following the diagnosis of anti-factor H antibody-associated complement-mediated atypical haemolytic uraemic syndrome, the patient was initiated on **therapeutic plasma exchange (TPE)** and immunosuppressive therapy. She underwent **five sessions of therapeutic plasma exchange**, with **fresh frozen plasma (FFP)** used as the replacement fluid. Two additional units of FFP were administered during the course of plasma exchange.

Immunosuppressive therapy consisted of **intravenous methylprednisolone 500 mg once daily for 5 consecutive days**, followed by **oral prednisolone at 1 mg/kg/day**. The corticosteroid dose was gradually tapered according to the patient's clinical and laboratory response, and she remained on **oral prednisolone 30 mg/day** at the latest follow-up.

Supportive management included transfusion of **two units of packed red blood cells** for severe anaemia. **Platelet transfusions were not administered**, as there was no active bleeding or other clinical indication. Hypertension was managed with a **nicardipine oral** achieving satisfactory blood pressure control. Renal function, urine output, complete blood counts and markers of haemolysis were monitored serially throughout the hospital stay.

Eculizumab was not administered because it was unavailable at our institution. The patient showed progressive clinical, haematological and renal improvement following therapeutic plasma exchange and corticosteroid therapy.

Outcome and follow-up

The patient demonstrated progressive clinical improvement following therapeutic plasma exchange and corticosteroid therapy. Haematological parameters improved steadily, with recovery of the platelet count

from **58 × 10⁹/L** at presentation to **150 × 10⁹/L** at discharge. Renal function also improved significantly, with serum creatinine decreasing from a peak of **2.0 mg/dL** to **0.6 mg/dL**. Blood pressure was well controlled with treatment and measured **100/60 mmHg** at the time of discharge.

The patient remained clinically stable without neurological complications or the need for renal replacement therapy during her hospital stay. She was discharged on **oral prednisolone (1 mg/kg/day)** with advice for gradual tapering under close clinical supervision. At the latest follow-up, she remained on **oral prednisolone 30 mg/day**, with stable renal function, normal platelet count and no evidence of disease relapse.

The patient continues to undergo regular outpatient follow-up with periodic monitoring of complete blood counts, renal function, urine protein excretion and blood pressure to detect any recurrence of disease activity and to guide further tapering of corticosteroid therapy.

Discussion

Atypical haemolytic uraemic syndrome (aHUS) is a rare but severe form of thrombotic microangiopathy resulting from dysregulation of the alternative complement pathway. Unlike Shiga toxin-producing haemolytic uraemic syndrome (STEC-HUS), which is triggered by bacterial toxins, aHUS is characterised by persistent complement activation leading to endothelial injury, platelet activation and widespread formation of platelet-rich microthrombi. The resulting microvascular occlusion predominantly affects the kidneys but may also involve the central nervous system, heart and gastrointestinal tract. Without prompt diagnosis and treatment, aHUS is associated with substantial morbidity, including irreversible kidney injury, progression to end-stage kidney disease and death. Recent outcome studies further emphasize the importance of early diagnosis and treatment to preserve renal function (13, 14).

Anti-factor H antibody-associated aHUS represents a distinct acquired subtype of complement-mediated thrombotic microangiopathy and accounts for approximately 5–25% of paediatric cases, with a higher prevalence reported from South Asia. Autoantibodies directed against complement factor H impair its ability to regulate the alternative complement pathway, resulting in uncontrolled complement activation on endothelial surfaces. Although reduced serum C3 levels are frequently observed, normal complement concentrations do not exclude the diagnosis, as demonstrated in our patient. Therefore, measurement of anti-factor H antibodies should be considered in all children presenting with thrombotic microangiopathy, irrespective of complement levels.

A characteristic feature of anti-factor H antibody-associated aHUS is its strong association with homozygous deletion of the *CFHR1* and *CFHR3* genes. These genes encode complement factor H-related proteins involved in immune tolerance and complement regulation.

Homozygous deletion of *CFHR1–CFHR3* is thought to predispose susceptible individuals to the development of anti-factor H autoantibodies through loss of immune tolerance. In our patient, the markedly elevated anti-factor H antibody titre (18,224 U/mL), together with whole-exome sequencing

demonstrating homozygous *CFHR1–CFHR3* deletion, provided strong evidence supporting the diagnosis of complement-mediated aHUS. This combination of immunological and genetic findings has important implications for confirming the diagnosis, assessing the risk of relapse and guiding long-term management. The clinical characteristics of anti-factor H antibody-associated aHUS have been comprehensively described previously (17).

The differential diagnosis of thrombotic microangiopathy in children includes Shiga toxin-producing haemolytic uraemic syndrome (STEC-HUS), thrombotic thrombocytopenic purpura (TTP), disseminated intravascular coagulation (DIC), and secondary thrombotic microangiopathies associated with autoimmune diseases, infections or medications. In the present case, STEC-HUS was considered unlikely because there was no preceding diarrhoeal illness and stool testing for Shiga toxin-producing organisms was negative. Autoimmune causes were excluded by a negative antinuclear antibody test and the absence of clinical features suggestive of connective tissue disease. Although ADAMTS13 activity could not be measured because the test was unavailable at our institution, the absence of neurological manifestations, together with the markedly elevated anti-factor H antibody titre and confirmation of a homozygous *CFHR1–CFHR3* deletion, strongly supported the diagnosis of anti-factor H antibody-associated aHUS rather than TTP.

An important feature of this case was the presence of **normal serum C3 and C4 levels** despite evidence of complement-mediated disease. Although hypocomplementaemia is commonly described in patients with aHUS, normal complement levels do not exclude the diagnosis because complement activation may be localised to the endothelial surface without causing significant depletion of circulating complement proteins. Therefore, anti-factor H antibody testing and genetic evaluation should be pursued whenever clinical suspicion remains high, irrespective of serum complement levels. This case highlights the importance of integrating clinical, immunological and genetic findings to establish an accurate diagnosis.

Therapeutic plasma exchange remains a cornerstone of treatment for anti-factor H antibody-associated aHUS, particularly in settings where complement inhibitors are unavailable. Plasma exchange removes circulating anti-factor H autoantibodies while simultaneously replacing functional complement factor H, thereby restoring regulation of the alternative complement pathway. Corticosteroids are administered concurrently to suppress ongoing autoantibody production and reduce the risk of relapse. In our patient, early initiation of therapeutic plasma exchange combined with corticosteroid therapy resulted in rapid haematological recovery, improvement in renal function and complete clinical stabilisation without the need for renal replacement therapy.

The introduction of terminal complement inhibitors, particularly **eculizumab**, has transformed the management of complement-mediated aHUS by preventing ongoing complement activation and reducing the risk of disease recurrence. Current international guidelines recommend complement inhibition as first-line therapy whenever available. However, limited availability and high cost remain major barriers in many low- and middle-income countries. In our patient, eculizumab was not available;

nevertheless, early initiation of therapeutic plasma exchange combined with corticosteroid therapy resulted in complete haematological recovery and restoration of renal function. This favourable outcome highlights that conventional therapy remains an effective treatment option in resource-limited settings, particularly when instituted promptly.

Patients with anti-factor H antibody-associated aHUS remain at risk of relapse because circulating autoantibodies may persist despite clinical remission. Therefore, long-term follow-up is essential and should include periodic assessment of complete blood counts, renal function, blood pressure, urinalysis and, where available, serial measurement of anti-factor H antibody titres. Gradual tapering of immunosuppressive therapy should be guided by both clinical response and laboratory findings to minimise the risk of recurrence. Emerging biomarkers may also assist in disease monitoring and relapse assessment (19).

The present case is noteworthy because it demonstrates several characteristic but uncommon features of anti-factor H antibody-associated aHUS. The coexistence of a markedly elevated anti-factor H antibody titre with a **genetically confirmed homozygous CFHR1–CFHR3 deletion** provides strong evidence for complement-mediated disease. Furthermore, the patient achieved an excellent clinical outcome with therapeutic plasma exchange and corticosteroids despite the unavailability of complement inhibitor therapy. This case also emphasises that **normal serum complement levels do not exclude complement-mediated aHUS**, reinforcing the importance of comprehensive immunological and genetic evaluation in children presenting with thrombotic microangiopathy.

In conclusion, this case highlights the importance of maintaining a high index of suspicion for anti-factor H antibody-associated aHUS in children presenting with microangiopathic haemolytic anaemia, thrombocytopenia and acute kidney injury. Early diagnosis through integration of clinical findings, immunological testing and genetic analysis allows timely initiation of appropriate therapy and can lead to favourable haematological and renal outcomes. Increased awareness of this rare but treatable condition may facilitate earlier recognition and improve patient prognosis, particularly in resource-constrained settings.

Learning points

- Anti-factor H antibody-associated atypical haemolytic uraemic syndrome (aHUS) should be considered in children presenting with the triad of microangiopathic haemolytic anaemia, thrombocytopenia and acute kidney injury, even in the absence of preceding diarrhoeal illness.
- Normal serum complement (C3 and C4) levels do not exclude complement-mediated aHUS; anti-factor H antibody testing and genetic analysis are essential when clinical suspicion is high.
- Homozygous deletion of the CFHR1 and CFHR3 genes is strongly associated with anti-factor H antibody-associated aHUS and supports the diagnosis.
- Early initiation of therapeutic plasma exchange combined with corticosteroid therapy can result in favourable haematological and renal recovery, particularly in resource-limited settings where

complement inhibitors are unavailable.

- Long-term follow-up is essential because patients remain at risk of relapse and require ongoing monitoring of renal function, blood pressure and haematological parameters.

Patient consent for publication

Written informed consent for publication of this case report and any accompanying images was obtained from the patient's parent/legal guardian. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

Declarations

Ethics and consent to participate

Written informed consent was obtained from the patient's parent/legal guardian. Ethical approval was not required for a single case report as per institutional policy.

Consent to publish

Written informed consent for publication was obtained from the patient's parent/legal guardian.

Availability of data and materials

All data generated or analysed during this study are included in this published article.

Competing interests

The authors declare that they have no competing interests.

Funding

Not applicable.

Authors' contributions

Dr. P. Arun Pandiyan managed the patient, collected the data and drafted the manuscript. Dr. Srinivasan R supervised the manuscript and critically revised it. Dr. Benjamin Sagayaraj contributed to patient management and manuscript review. All authors read and approved the final manuscript.

Acknowledgements

Not applicable.

Authors' information

References

1. Noris M, Remuzzi G. *Atypical hemolytic-uremic syndrome*. N Engl J Med.
2. Loirat C, Fakhouri F, Ariceta G, et al. *An international consensus approach to the management of atypical HUS in children*. Pediatr Nephrol.
3. Goodship THJ, Cook HT, Fakhouri F, et al. *Atypical hemolytic uremic syndrome and C3 glomerulopathy: conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference*. Kidney Int.
4. Dragon-Durey MA, et al. Anti-factor H autoantibodies in aHUS.
5. Józsi M, et al. CFHR1/CFHR3 deletion and anti-factor H antibodies.
6. Hofer J, et al. Anti-factor H antibody-associated HUS.
7. Fakhouri F, et al. Genetics of aHUS.
8. Kavanagh D, et al. Complement dysregulation in aHUS.
9. Campistol JM, et al. Treatment recommendations.
10. Legendre CM, et al. Eculizumab in aHUS
11. Noris M, Remuzzi G, Loirat C, Fakhouri F, Ariceta G. *Atypical hemolytic uremic syndrome and C3 glomerulopathy: conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference*. Kidney Int. 4. Dragon-Durey MA, et al. Anti-factor H autoantibodies in aHUS. 5. Józsi M, et al. CFHR1/CFHR3 deletion and anti-factor H antibodies. 6. Hofer J, et al. Anti-factor H antibody-associated HUS. 7. Fakhouri F, et al. Genetics of aHUS. Pediatr Nephrol. 2.
12. George JN, Nester CM. Syndromes of thrombotic microangiopathy. New England Journal of Medicine. 2014;371(7):654–66.
13. Maisons V, Duval A, Mesnard L, Frimat M, Fakhouri F, Grangé S, Servais A, Cartery C, Fauchier L, Coppo P, Titeca-Beauport D. Assessment of epidemiology and outcomes of adult patients with kidney-limited thrombotic microangiopathies. Kidney international. 2024;105(5):1100–12.
14. Schwimmer J, Nadasdy TA, Spitalnik PF, Kaplan KL, Zand MS. De novo thrombotic microangiopathy in renal transplant recipients: a comparison of hemolytic uremic syndrome with localized renal thrombotic microangiopathy. American journal of kidney diseases. 2003;41(2):471–9.
15. Liszewski MK, Java A, Schramm EC, Atkinson JP. Complement dysregulation and disease: insights from contemporary genetics. Annual Review of Pathology: Mechanisms of Disease. 2017;12(1):25–52.
16. de Córdoba SR, Hidalgo MS, Pinto S, Tortajada A. Genetics of atypical hemolytic uremic syndrome (aHUS). In Seminars in thrombosis and hemostasis 2014 Jun (Vol. 40, No. 04, pp. 422–430). Thieme Medical Publishers.

17. Dragon-Durey MA, Sethi SK, Bagga A, Blanc C, Blouin J, Ranchin B, André JL, Takagi N, Cheong H, Hari P, Le Quintrec M. Clinical features of anti-factor H autoantibody–associated hemolytic uremic syndrome. *Journal of the American Society of Nephrology*. 2010;21(12):2180–7.
18. Loirat C, Frémeaux-Bacchi V. Anti-factor H autoantibody-associated hemolytic uremic syndrome: the earlier diagnosed and treated, the better. *Kidney International*. 2014 May 1;85(5):1019-22.
19. Raina R, Sethi SK, Dragon-Durey MA, Khooblal A, Sharma D, Khandelwal P, Shapiro R, Boyer O, Yap HK, Bagga A, Licht C. Systematic review of atypical hemolytic uremic syndrome biomarkers. *Pediatric Nephrology*. 2022;37(7):1479–93.
20. Java A, Pozzi N, Love-Gregory LD, Heusel JW, Sung YJ, Hu Z, Bertram P, Liszewski MK, Cline LM, Ren Z, Atkinson JP. A multimodality approach to assessing factor I genetic variants in atypical hemolytic uremic syndrome. *Kidney international reports*. 2019;4(7):1007–17.