syndrome. Eur J Endocrinol. 2012;166:537-42.
6. Gideon DS, Rainer W, Werner A. Precocious pseudopuberty due to autonomous ovarian cysts: A report of ten cases and long-term follow-up. Hormones. 2008; 7:170-4.
7. Jean CC, Juliane L. Precocious Puberty. N Engl J Med. 2008;358:2366-77.
8. Nabhan ZM, West KW, Eugster EA. Oophorectomy in McCune-Albright syndrome: a case of mistaken identity. J Pediatr Surg. 2007;42:1578.
9. Schultz KAP, Schneider DT, Pashankar F, Ross J, Frazier L. Management of ovarian and testicular sex cord-stromal tumors in children and adolescents. J Pediatr Hematol Oncol. 2012;34:S55-S63.
10. Haroon NN, Agarwal G, Pandey R, Dabadghao P. Juvenile granulose cell tumour presenting as isosexual precocious puberty: A case report and review of literature. Indian J Endocrinol Metab. 2013;17:157-9.

Plasma Exchanges and Immunosuppression for Anti-complement Factor H Associated Hemolytic Uremic Syndrome

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Background: Atypical hemolytic uremic syndrome associated with autoantibodies to complement factor H is an important cause of acute kidney injury; most patients require dialysis and are at risk of progressive renal failure. **Case Characteristics:** 7 patients with gastrointestinal symptoms, acute kidney injury, thrombotic microangiopathy and elevated levels of anti-complement factor H antibodies. **Intervention**: Prompt initiation of plasma exchanges and immunosuppression. **Outcome**: Remission of hematological and kidney functions. **Message**: Prompt and specific management of antibody associated hemolytic uremic syndrome is associated with favorable outcome.

Keywords: *Corticosteroids, Hemolysis, Renal failure.*

Autoantibodies to complement factor H (CFH) are an important cause of atypical hemolytic uremic syndrome (HUS) in children, comprising 10-20% patients in cohorts from Europe and UK [1-3]. In a 6-year multicenter study on 246 patients with atypical HUS from India, we found high titers of anti-CFH antibodies in 56% cases [4]. Patients with anti-CFH associated HUS presented late, and had a relatively severe illness with prolonged oligoanuria, severe hypertension and prominent extra renal manifestations. The majority required renal replacement therapy and one-third had progressive kidney failure [3]. Although speculated that an infectious agent triggers formation of these antibodies in genetically susceptible hosts, no organism was identified.

During the months of January and February 2014, 7 patients were referred to us with HUS associated with anti-CFH antibodies. Given that this center normally takes care of 7-10 new patients with HUS annually, the increase in number of patients was unusual. We report their clinical features and outcomes.

CASE REPORTS

The clinical and laboratory features in 7 patients (3 girls), 5- to 11-yr-old, are shown in ***Table* I**. These patients presented with history of abdominal pain and vomiting followed by sudden onset of pallor and variable degree of jaundice and oliguria; none had hypertension. The diagnosis of HUS was based on presence of schistocytes in the peripheral smear, thrombocytopenia and elevated blood levels of creatinine. Six patients showed hypokalemia that persisted for 3-5 days. There was no history of diarrhea or any significant family history in all patients. Serology for leptospira, enteric fever, hepatitis A and E, and antinuclear antibody and antineutrophil cytoplasmic antibody were negative. Malarial parasite was not seen on smear examination. Anti-CFH antibody titers, estimated using ELISA [3], ranged between 880 and 16380 (normal <150) AU/ml. Low levels of complement C3 were present in six patients.

Following the diagnosis of HUS, plasma exchanges (filtration based, 1.5-volume) using fresh frozen plasma were initiated at a median of 9 days from onset of the illness. The plasma was dark brown during the first few exchanges, suggesting severe intravascular hemolysis. Each patient received daily plasma exchanges initially until hematological remission, followed by alternate day and finally twice weekly for total of 15-20 exchanges. The severity of renal failure was variable; peak creatinine

TABLE I CLINICAL AND BIOCHEMICAL PROFILE IN PATIENTS WITH ANTI-COMPLEMENT FACTOR H (CFH) ANTIBODY ASSOCIATED HEMOLYTIC UREMIC SYNDROME

	Patient 1	*Patient 2*	*Patient 3*	*Patient 4*	*Patient 5*	*Patient 6*	*Patient 7*
Age, sex	5-yr, girl	5-yr, boy	8.5-yr, boy	6-yr, boy	10-yr, girl	11-yr, boy	7-yr, girl
Residence	New Delhi	Amethi	New Delhi	New Delhi	Muzaffarnagar	Ambala	New Delhi
Symptoms	Pallor	Pallor, cola color urine, oliguria	Jaundice, melena	Pallor, jaundice oliguria	Abdominal pain, vomiting	Pallor, jaundice; oliguria	Oliguria, cola color urine, pallor
Hemoglobin (g/dL)	5.1	6	4.9	4.9	7.2	6.0	4.3
Reticulocytes	6%	8%	11%	7%	2%	7%	4%
LDH (IU/L)	3600	980	2865	2336	4350	2664	887
Platelets (/μl)	82000	32000	56000	44000	80000	101000	50000
Creatinine (mg/dL)	1.7	4.4	2.7	2.4	2.3	6.7	4.1
Potassium (mEq/L)	2.4	2.6	3.1	2.9	1.5	2.9	3.9
Proteinuria	3+	3+	3+	3+	3+	4+	2+
AST/ALT (IU/L)	60/28	196/60	154/98	91/11	200/35	76/39	114/40
Bilirubin (mg/dL)	0.5	2.6	1.6	1.4	1.0	1.0	0.5
Complement C3, mg/dl	71.4	39.1	150	70	66.1	75.2	68.5
Anti CFH antibody, AU/mL	2265	16380	880	1920	7535	2390	2900
Hemodialysis	Nil	2 sessions	Nil	Nil	Nil	3 sessions	2 sessions
Duration from onset to PEX	8 days	7 days	18 days	13 days	7 days	10 days	9 days
Duration to hematological remission	6 days	9 days	10 days	9 days	15 days	5 days	6 days
Follow up							
Creatinine	0.5 mg/dL;	0.5 mg/dL;	0.5 mg/dL;	0.5 mg/dL;	0.4 mg/dL;	0.6 mg/dL;	0.7 mg/dL;
Proteinuria	2+	Nil	1+	1+	2+	2+	2+
Hypertension	Stage 1	Absent	Stage 1	Stage 2	Absent	Stage 1	Stage 1

• *AST: aspartate aminotransferase, ALT: alanine aminotransferase, AU: arbitrary units, LDH: lactate dehydrogenase, PEX: plasma exchange.*

ranged from 1.7-6.7 mg/dL. Transient hemodialysis was required in three patients. Following detection of anti-CFH antibodies, patients also received a combination of oral prednisolone (2 mg/kg/d; tapered over 4 weeks) and either intravenous cyclophosphamide (500 mg/m^2 3-weekly for 5 doses) or intravenous rituximab (375 mg/m^2 weekly for 2 doses). Patient 6 did not receive immunosuppressive agents initially because of suspected hepatitis C infection (positive qualitative PCR). Since he continued to show high antibody titers, therapy with prednisolone was given 3 months later, following two negative PCR results and negative serology for hepatitis C. During follow up, ranging between 3-4 months, 5 patients showed hypertension; blood levels of creatinine were normal and there was variable proteinuria.

DISCUSSION

While most cases of HUS, an important cause of acute kidney injury in children, are secondary to shigatoxin-mediated endothelial damage, atypical HUS is caused by dysregulation of the alternative complement pathway, with mutations in genes encoding regulatory proteins such as CFH, CFI and CD46 [5]. HUS in association with anti-CFH autoantibodies is a distinct subgroup occurring on a background of homozygous deletions in the *CFHR1* gene [5]. These antibodies bind to multiple epitopes on CFH, impairing its regulatory function [6]. The condition affects children, 5-14 yr-old, and has a relapsing course with 30-40% risk of end stage renal failure [2,3]. In our earlier series of 138 patients with anti-CFH antibody associated HUS [4], the illness was severe with majority requiring acute renal replacement therapy and one-third progressing to chronic kidney disease stage 5.

Compared to median of 10 days oliguria in prior reports [3,4], these patients presented early, before or within 48-hr of onset of oliguria. Six patients had hypokalemia, contrary to expected in acute kidney injury. While this was attributed to poor intake and vomiting during the prodrome, none of the patients was dehydrated or undernourished at admission. Blood pressure was normal at presentation in all patients, in contrast to hypertension in 60-68% patients in previous reports [2-4]. The later detection of hypertension in five patients was consistent with the diagnosis of HUS. While three patients in the present report required dialysis and all showed favorable short-term outcome, 86% patients in the nationwide report had required a median of four-weeks of dialysis and 29.5% were dialysis-dependent on follow up [4]. We previously showed that delayed initiation of plasma exchange (≥17 days beyond onset) increased adverse outcomes by 6-10 fold, while combination of immunosuppression and plasma exchanges reduced the risk 5-9 fold [4]. The patients described herein received plasma exchanges at median 9 days from onset, suggesting that prompt diagnosis and rapid treatment result in favorable outcomes.

All patients had a gastrointestinal prodrome and elevated transaminases, suggesting a common infectious trigger. A predilection for winter months was reported among Indian children with HUS [4], supporting a 'two hit hypothesis' where a microbial agent triggered generation of anti-CFH antibodies in patients with homozygous deletion of *CFHR1*. Since the allele frequency of *CFHR1* deletion is similar across the world [2,7], a preponderance of the infectious trigger might account for an increased proportion of patients with anti-CFH antibody associated HUS in our country. Further studies are necessary to define the inherited and environmental mechanisms for development of these antibodies.

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REFERENCES

1. Moore I, Strain L, Pappworth I, Kavanagh D, Barlow PN, Herbert AP, *et al*. Association of factor H autoantibodies with deletions of CFHR1, CFHR3, CFHR4 and with mutations in CFH, CFI, CD46 and C3 in patients with atypical hemolytic uremic syndrome. Blood. 2010;115:379-87.
2. Hofer J, Janecke AR, Zimmerhackl LB, Riedl M, Rosales A, Giner T, *et al*. Complement factor H-related protein 1 deficiency and factor H antibodies in pediatric patients with atypical hemolytic uremic syndrome. Clin J Am Soc Nephrol. 2013;8:407-15.
3. Dragon-Durey MA, Sethi SK, Bagga A, Blanc C, Blouin J, Ranchin B, *et al*. Clinical features of anti-factor H autoantibody-associated hemolytic uremic syndrome. J Am Soc Nephrol. 2010;21:2180-7.
4. Sinha A, Gulati A, Saini S, Blanc C, Gupta A, Gurjar BS, *et al*. Prompt plasma exchanges and immunosuppressive treatment improves the outcomes of anti-factor H autoantibody-associated hemolytic uremic syndrome in children. Kidney Int. 2014;85:1151-60.
5. Loirat C, Fremeaux-Bacchi V. Atypical hemolytic uremic syndrome. Orphanet J Rare Dis. 2011;6:60.
6. Blanc C, Roumenina LT, Ashraf Y, Hyvarinen S, Sethi SK, Ranchin B, *et al*. Overall neutralization of complement factor H by autoantibodies in the acute phase of the autoimmune form of atypical hemolytic uremic syndrome. J Immunol. 2012;189:3528-37.
7. Abarrategui-Garrido C, Martinez-Barricarte R, Lopez-Trascasa M, de Cordoba SR, Sanchez-Corral P. Characterization of complement factor H-related (CFHR) proteins in plasma reveals novel genetic variations of CFHR1 associated with atypical hemolytic uremic syndrome. Blood. 2009;114:4261-71.