# Myriad complement defects in atypical hemolytic uremic syndrome and short term outcome in the absence of eculizumab.

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March 07, 2024

**Abstract**

An amiss complement pathway can cause atypical hemolytic uremic syndrome (aHUS) with microangiopathic hemolytic anemia, thrombocytopenia and acute kidney injury. An observational study to understand complement abnormalities and outcome among pediatric aHUS in absence of targeted therapy was done. We enrolled 35 children from July 2017 to December 2018. Besides recording clinical details, hematological and renal parameters were assessed. Complement analysis included a one-time evaluation of C3, C4, anti-factor H antibody (VIDITEST human ELISA kit), factor H, I, B (Sinogeneclon ltd.) and CD46/membrane co-factor protein (MCP) (flow cytometry). SPSS version 23 (Chicago, IL) was used for analysis. Median age was 49 months (sex ratio of 1.7:1). Hypertension was noted in 74.2%(26) and central nervous system involvement in 34.3%(12). At admission, mean hemoglobin was 6.7±1.8 g/dL, median platelet count was 78x109 cells/L(38,101) and median eGFR was 11.91ml/min/1.73m2(6.5, 21.3). C3 was low in 57% (20), while 25.7% (9) had low C4 levels. Anti-factor H antibody was positive in 44% (15). Low expression of MCP in leucocytes was seen in 26.7% (8). Further, 3 had low factor H and high factor B respectively, while 2 had low factor I levels. Plasma-therapy was initiated in 65.7%. Remission was noted in 48.5% (17), 31.4% (11) died and others discontinued treatment. Though anti-factor H antibody is the most common followed closely by low MCP expression, abnormal levels of different complement proteins were observed. Outcome was dismal without eculizumab. We recommend comprehensive complement analysis in pediatric aHUS. Development and availability of targeted therapy remains unquestionable.

## Introduction:

Defect in alternate complement pathway can cause atypical hemolytic uremic syndrome (aHUS) which is the triad of non-immune haemolytic anemia, thrombocytopenia and acute kidney injury (AKI). Mutation in regulators like factor H (FH), factor I (FI), membrane cofactor protein (MCP)/ CD46 or activators like FB or C3, remain the major underlying pathogenesis. Further, there have been studies to suggest dual complement abnormalities [1-4]. Moreover, children with aHUS present with varied manifestations ranging from renal to extra-renal manifestations like central nervous system (CNS), hepatic and cardiac involvement. Although certain complement defects like MCP, anti-FH antibody associated HUS, have a phenotypic relationship in clinical manifestations and natural history, it is not applicable to most. Hence, we tried to study the spectrum of complement abnormalities, presentation and short term outcome in pediatric aHUS.

## Methods:

We performed a prospective observational study after obtaining an institutional ethical clearance (INT/IEC/2017/000299). Informed written consent and wherever applicable, assent was taken from pa-

rents and patients. Children who presented to our centre and diagnosed as HUS were screened. Infection associated and secondary causes of HUS (HIV, malignancy, cobalamin deficiency, drug induced, autoimmune diseases) were ruled out. All those with aHUS were enrolled in the study.

Relevant history was documented. Examination was done at enrolment and blood pressure was staged according to AAP guidelines.[2] Investigations including complete blood count (SYSMEX XN-1000; Japan) and renal function was performed at three points of care namely at admission, minimum value reached and maximum value achieved during hospital stay. We categorized anemia according to WHO classification. [3] Children who had platelet count less than 150 x $10^9$cells/L were considered to have thrombocytopenia, which was categorized as mild (100-150x$10^9$/L), moderate (50-100x$10^9$/L) and severe (<50x$10^9$/L). Fragmented red blood cells or schistocytes were documented according to the standards of ICSH recommendations by an expert Hematopathologist. [4] Lactate dehydrogenase (LDH) level was also recorded, >500 U/L indicative of hemolysis. AKI was staged according to KDIGO guidelines. [5] Estimated glomerular filtration rate (eGFR) was calculated using bedside modified Schwartz formula which utilizes length/ height of child in centimetre and serum creatinine values in milligram per decilitre. [6] Urine routine microscopy was performed to look for microscopic hematuria. Proteinuria was analysed as negative, non-nephrotic and nephrotic range.

Human immunodeficiency virus (HIV) serology, anti-nuclear antibodies (ANA), and blood culture were done to rule out secondary causes like infection triggered or autoimmune etiologies. Stool culture and STEC-PCR was performed if there was a prodrome of diarrhea to ensure that STEC HUS was not included.

All children with aHUS were worked up for underlying complement defects

(i). Complement C3 and C4 was performed by end-point nephelometry. Interpretation was according to age-wise normative data which were available from our immunology laboratory.

(ii). Anti-FH antibody (IgG) testing was done by ELISA method using VIDITEST ELISA kit (Intra-Assay: CV < 6%, Inter-Assay <10%; Detection limit- 0.6 AU/ml). 26 AU/ml was taken as the cut off.

(iii).Factor B, H and I were also done by ELISA according to the manufacturers (SinoGeneclon Ltd.) described method.

(vi).CD46 {membrane co-factor protein (MCP)} was estimated by flow cytometry. The median fluorescent index was assessed by flow-cytometry in all the leucocytes (neutrophils, monocytes and lymphocytes). It was measured in both stimulated and unstimulated phase. Later δ MFI and staining index were calculated for standardization.

For analysis of complement parameters by flow-cytometry, 40 healthy children were also analysed and reference range was derived from the mean of δMFI expression of those 40 healthy controls.

*Statistical analysis:* Data was analyzed using SPSS Version 23 (Chicago, IL). Standard statistical tests were used for analysis. All quantitative data were analyzed for their normal distribution using tests of normality (Kolmogrov test). Descriptive statistics was used for baseline comparison. For normally distributed data (platelet count at admission, urea at admission, C3, C4) independent t-test was used for comparison of means. For skewed data (age, creatinine) non-parametric test was used for comparison of medians. For continuous independent variables, unpaired t test was performed while for categorical variables, Chi-square tests or Fisher's Exact tests (if cell frequency < 5), was used.

**Results:**

Forty children were screened at enrolment. 5 children were excluded (1- diagnosed to have malignancy; 2 children- blood culture positive with DIC; 2 children- parents not giving consent). 35 children who fulfilled the inclusion criteria were enrolled and were further investigated.

Median age was 49 months with IQR of 9 to 90 months. The highest age noted was 140 months while the lowest, 1 month. Majority of patients were more than 24 months (60%). Out of 35 children studied, 62.9% were males with a sex ratio of 1.7: 1. While decreased urine output was the most common presentation,

pallor was the most common clinical finding. (Table 1) Details of symptoms at presentation are described in Figure 1. Severe anemia was noted in 88.6% (31) and severe thrombocytopenia in 71.4% (25). AKI Stage 3 was seen in 80% (28) at presentation though 91.4% (32) developed it during the course. Hematuria was observed in 59.9% (21) children, among which 2 children had gross hematuria. Proteinuria was present in 27children, out of which 12 (34.3%) had nephrotic range. Six out of twelve children who showed a diarrhoea prodrome had their stools evaluated for STEC PCR to rule out STEC HUS, which were negative. Thirteen children had positive ANA (speckled pattern). Among those with positive ANA, ds-DNA was done in 3 children which were normal.

C3 and C4 levels were analyzed in all 35 patients among whom 57.1% (20) had low C3 and 25.7 % (9) had low C4 levels. Both C3 and C4 levels were low in 6 children. Five children who had low C3 and C4 were also negative for ANA, but one had speckled pattern ANA positivity. Mean C3 and C4 levels were 75 ± 26 mg/L and 22 ± 8 mg/L respectively. Three children had low FH levels with no relation to anti-FH antibody. Two children had low FI levels while 3 children had high FB levels. Anti-FH antibody levels were elevated in 44% (15) of children with a mean anti-FH titre level of 137.68 ± 50.1 AU/ml. Low CD46 expression assessed by median fluorescent index in neutrophils, monocytes and lymphocytes was noted in 8 children. (Mean δMFI - 8311 ± 1415.5) [Figure 2]

25 children had hypertension that was controlled with a mean of 3 anti-hypertensive drugs. 7 of them exhibited hypertensive emergencies requiring parenteral anti-hypertensive drugs. 62.8% (22) required dialysis support. Plasmapheresis (PEX) was offered to all children and plasma infusion was tried in the very small infants where PEX was not feasible. PEX was performed in 16 children while plasma infusion was given in 7. Immunosuppression was initiated in children where possibility of anti-FH antibody HUS was considered. Most of these children were those who had already received plasma therapy.

Seventeen children (48.6%) improved in terms of hematological remission with or without renal improvement. Eighteen children (51.4%) had a negative outcome as death or withdrawal of care (lost to follow up).

On further analysis, younger children (less than 24 months) had more negative outcome (36.8%) than those more than 24 months (63.2%) ($p < 0.05$). The mean hemoglobin levels were always on a higher side among children who had later attained remission compared to those who did not, however it was not statistically significant.

**Discussion:**

Our study is one of the few trying to elaborate various complement abnormalities, presentation and outcome in pediatric aHUS, albeit in the absence of targeted therapy. While a myriad of mutations have been documented, yet the whole picture is still not as vivid as we want it to be. Besides, the phenotype association in different mutations is something that we need to understand further.

In our cohort, the median age of presentation was 49 months which was different from other studies where it is around 24 months [7-10].The reason for this difference could be that previous studies included more of infection associated HUS, especially STEC HUS, while our study population had included only aHUS. However, the possibility remains that in India, HUS is more common in older age group. A retrospective study by Aditi et al. in children with anti-FH antibody HUS observed that mean age was 8.4 ± 4.1 years [11].

It was a male predominant study similar to that done by Srivastava et al. [7]. However, a lower sex ratio was noted in western countries with a ratio of 0.9 [12]. This difference could be due to the male predominant society, though the possibility that boys have a more propensity for these abnormalities remains.

Oliguria was the most common presentation (71.4%) followed by progressive pallor (48.6%) as HUS itself is a triad of hemolytic anemia, thrombocytopenia and AKI. One-third children had loose stools (1 with bloody diarrhea) as prodromal feature suggesting, loose stools as a prodromal feature can also be noted in aHUS as shown in previous studies [11,13]. Seizure was the commonest extra-renal presentation similar to that observed by Hughes et al. [8]. Neurological involvement might be due to disease as such or can be secondary

due to sequel of disease like azotemia, electrolyte imbalances and posterior reversible encephalopathy due to hypertension.

Prevalence of acute hypertension in our cohort was similar to that observed by Hughes et al. They documented that 61% had hypertension. However, other studies showed an incidence of 15–30% [7, 14]. This may be due to the fact that STEC HUS is known to have less severe manifestations. Hypertension in HUS is mainly due to pre-glomerular vessel involvement which causes a break in renin angiotensin axis and result in hyperreninemic state aggravating hypertension [15].

Severe anemia was noted initially in half, however, because of on-going hemolysis, 88% subsequently had severe anemia. Similar haemoglobin levels were noted in other studies where children were assessed retrospectively after being diagnosed as HUS [8,9]. Anemia in HUS is mainly due to intravascular hemolysis caused by stress of constricted small vessels and microthrombi formed due to endothelial damage. In our study, there was no correlation between levels of haemoglobin and outcome, though it was not powered for the same. Thus, further larger studies are required. Two-third children had moderate to many schistocytes in peripheral smear suggesting severe hemolysis. Studies have been published for standardization of schistocyte counting and reporting, that may help in decreasing the observer bias [16].

Severe thrombocytopenia was noted in one-third of children at admission but there was a two-fold decrease during the course. Similar results were noted in other studies [7-9]. This is due to excessive consumption of platelets in endothelial damage induced fibrin and platelet thrombi formation.

In our study, 80% children presented with AKI stage 3. Staging of AKI helps in prognostication and assessment of outcome. Although 93% children had AKI stage 3 during hospital course, 14 children showed recovery.

Proteinuria was found consistently in studies where urine analysis was performed [16]. It can result due to podocyte dysfunction caused by activated alternate complement pathway. Interestingly, nephrotic range proteinuria was noted in a higher proportion (34.3%) in our cohort compared to other studies [7]. Hematuria was noted in 60% children which was consistent with other studies [9]. It is due to complement mediated damage to endothelium of glomerular arterioles. Hematuria and proteinuria suggests glomerular involvement. Doorn et al, reported a child who was initially treated as MPGN and was later diagnosed to have HUS because of recurrent relapses [17].

We observed that C3 was low in 57.1% and C4 in 25.7 % of our study cases. Kaplan et al., and Stuthlinger et al., [18, 19] have described hypo-complementemia in HUS. They explained that low C3 is due to intravascular activation of classical complement pathway. This might also explain low C4 levels, as it is part of classical pathway. Similar data of low C4 levels were noted in a study by Song et al., where he assessed C4 levels in anti-FH antibody associated HUS children [20]. Both C3 and C4 can be low in SLE which is a disease affecting classical pathway. All our 6 children who had low C3 and C4 were screened with ANA which was negative. Therefore, it maybe plausible that the classical pathway is activated in aHUS.

Further, three-fourth of the study population had abnormalities in at least one component of complement system. Anti-FH antibody HUS was found in 15 children (44%). This is different to a European study where only 22% children had anti-FH associated HUS [21]. However, it is similar from studies from India where it forms the predominant group [10].In our study, low CD46 expression which constituted 26.7% of study population was more compared to that by Khandelwal et al where 12.7% had CD46 defect [22]. However, this has to be confirmed with genetic mutation studies. Interestingly, three children in this sub-group also had elevated anti-FH levels which had been previously described in literature [22].

Treatment of HUS is based on etiology. In our study, children with suspicion of aHUS based on clinical presentation and investigations, especially antibody associated HUS, underwent plasma therapy if amenable. In India, as per literature, anti- FH antibody HUS is more common than other forms of atypical as well as STEC associated HUS [10]. Hence empirical treatment with PEX and immunotherapy was offered.

Almost all children who underwent PEX were initiated with immunosuppressive therapy which included

methylprednisolone followed by oral steroids and cyclophosphamide. It has been found that PEX followed by immunosuppression had a better renal outcome than immunosuppression alone in case of rapidly progressive glomerulonephritis [23]. Sana et al., observed that in anti-FH HUS too, early immunosuppression using cyclophosphamide pulse therapy along with PEX caused sustained remission, decreasing need of maintenance therapy [24].

Previous literature described a lower mortality rate of 25% after increased utility of plasma therapy in HUS [25, 26] and a French cohort reported only in 8.6% [27]. However, overall outcome of our cohort was worse. This could be due to many factors, but etiology, poor socio-economic status, affordability for PEX and non-availability of eculizumab could be important reasons. However, further larger studies are needed to assess prognostic factors.

Age of onset of illness is an important predictor for outcome of disease. Previous studies suggest that poor outcome is noted in children of younger age when compared to toddlers and school going age group [11]. Similarly, our study also showed a significant poorer outcome in younger children, especially in infants (p value $<0.01$). This age dependent outcome might be due to multiple factors like greater prevalence of familial HUS, difficult in amenability to treatment modalities like hemodialysis, PEX. Hence children with HUS presenting at less than 2 years needs to be worked up and diagnosed early. Further, there is a need for improving targeted therapy.

**Conclusion:** We observed that aHUS was more common in boys, with hypertension as a common presentation. While various complement abnormalities were detected, anti-FH antibody and low MCP expression seems to be common. Remission was seen only in half of the patients. We recommend a comprehensive complement analysis in pediatric aHUS as it has therapeutic implications.

**Declarations:**

**Acknowledgement:** We thank Mr Ravinder and Miss Kanika for helping us in the immunology laboratory.

**Funding-** The work was funded by the Post Graduate Institute of Medical Education and Research, Chandigarh via Special Research Grant 2017-18 for MD Thesis (L.P.480)

**Conflicts of interest/Competing interests-** None

**Ethics approval-** Approved by the Institute Ethics Committee (INT/IEC/2017/000299)

**Consent to participate-** Taken

**Consent for publication-** Taken

**Authors' contributions:** SG collected the data, analysed and wrote the first draft. AR, JKS, NT and JBAT performed the laboratory investigations, helped in their interpretation and added intellectual content to the manuscript. LD, RR and RH managed the patients, helped in collecting data, analysis and writing the manuscript. KT conceptualized the project, supervised the data collection, analysis and finalized the manuscript. All authors approved the final draft.

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**Table 1** : Baseline clinical and laboratory parameters in children with aHUS.

**Table 2** : Laboratory parameters at admission, at peak and at remission.

**Figure 1** : Proportion of symptoms at the time of presentation.

**Figure 2** : Complement abnormalities in our study population.

**Figure 3:** Analysis of CD46 (Membrane Cofactor Protein: MCP) expression on granulocytes of patient with HUS versus healthy control. Granulocytes were gated on FSC vs SSC dot plot. Autofluorescence is indicated by red (Control) and blue (patient) lines. Positivity for CD46 is shown by pink (patient) and green (control) lines. Median fluorescence intensity (MFI) is mentioned on the top of graph. Flowcytometry was performed within two hours of sample receiving.

**Table 1**

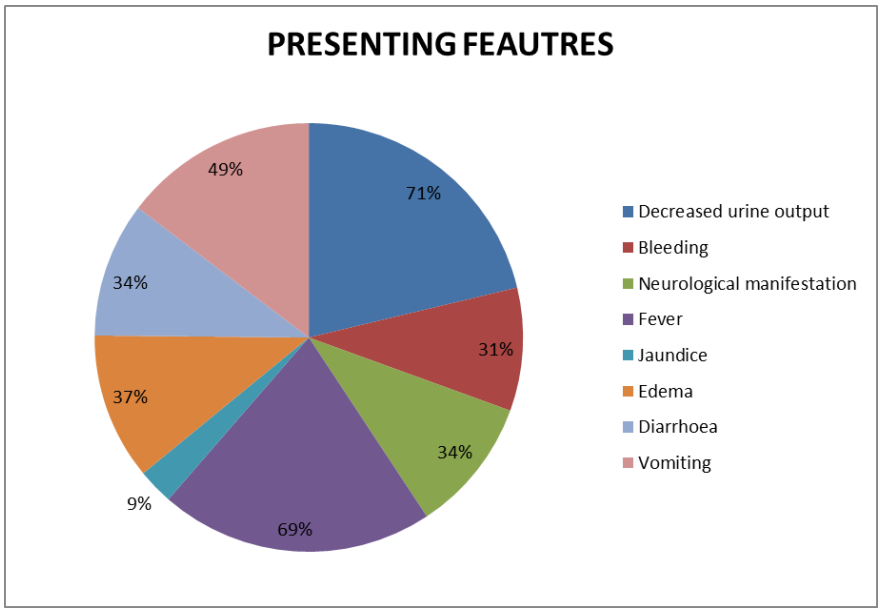
| Variables | Details |
|---|---|
| Boys | 62.9% (n-22) |
| Age [median (IQR)] | 49 months (9, 90) |
| Oliguria | 71.4% (n-25) |
| Pallor | 48.6% (n-17) |
| Edema | 37.1% (n-13) |
| Bleeding manifestation | 31.4% (n-11) |
| Prodromal symptoms Fever Diarrhoea Vomiting | 68.6% (n-24) 34.3% (n-12) 48.6% (n-17) |
| CNS manifestations | 34.3% (n-12) |
| Hypertension | 74.2% (n-26) |
| Hematuria | 59.9% (n-21) |
| Proteinuria Nephrotic range | 77.1% (n-27) 34.3% (n-12) |
| Hemoglobin (g/L) | 67 ± 18 |
| Platelet count (x $10^9$ cells/L | 78 (38, 101) |
| LDH (U/L) | 2966 ± 1973 |
| Blood urea (mmol/L) | 27.6 ± 13.9 |
| Serum creatinine (µmol/L) | 362.4 ± 274 |
| eGFR (ml/min/1.73 $m^2$) | 11.91 (6.5, 21.4) |
| C3 (mg/dL) | 75 ± 26 |

| Variables | Details |
|---|---|
| AFH antibody titers (AU/ml) | 137.68 ± 50.1 AU/ml |

**Table 2**

| Parameters | At admission | At maximum worsening | Best value attained |
|---|---|---|---|
| Hemoglobin (g/L) | 67 ± 18 | 56 ± 16 | 96 ± 21 |
| Platelet count (x $10^9$ cells/L) | 78 (38, 101) | 31 (14, 91) | 181 (103, 330) |
| LDH (U/L) | 2966 ± 1973 | 3194 ± 2106 | - |
| Blood urea (mmol/L) | 27.6 ± 13.9 | 35.5 ± 16.6 | 10.6 ( 6.1, 13.8) |
| Serum creatinine (µmol/L) | 362.4 ± 274 | 468.5 ± 300.6 | 67.1 (48.6, 265.2) |
| eGFR (ml/min/1.73 $m^2$) | 11.91 (6.5, 21.4) | 7.7 (5.68, 17.7) | 41.3 (15, 79.8) |

**Figure 1**



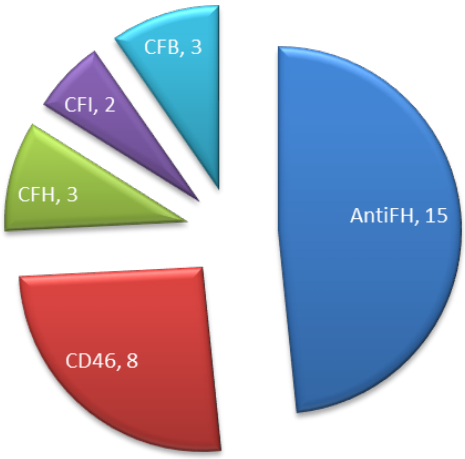



**Figure 2**

**Figure 3**