



Anti-Factor H Antibody Hemolytic Uremic Syndrome: A Disease in Need of “Make in India” Management

Hemolytic uremic syndrome (HUS) can occur as a result of complement pathway dysregulation. While mutations in the genes controlling complement activation account for most cases from Europe and America, the most common cause in India is the presence of antibodies to complement factor H (CFH).¹ While anti-CFH antibody HUS accounts for 5–24% of pediatric cases of complement-mediated HUS and about 19% of cases in adults in the Western countries, it is the predominant condition in Indian pediatric HUS patients,^{2,3} accounting for around 56% of all pediatric HUS patients in a nationwide study.

The study by Veeranki *et al.*⁴ in this issue of the journal from a single center in North India examine a retrospective cohort of pediatric and adult patients, 57.9% of whom had anti-factor H antibody-mediated disease. They followed up their patients for a median of 24 months. The incidence is almost the same as in the two multicenter pediatric studies published earlier. This would indicate that the disease may also be prevalent in Indian adults and must be suspected, detected, or ruled out, especially given the distinct treatment options and prognosis.

HUS in children, caused by antibodies to factor H has distinctive clinical characteristics, triggers, response to treatment, course, and prognosis. Puraswami *et al.*,² in the largest study in the world, described distinct characteristics of the disease, including changing trends in over 12 years. Compared with diseases caused by genetic variants, CFH-related HUS is characterized by an older age at onset, male predominance (though decreasing), shorter duration of oliguria and time to presentation, higher prevalence of transaminitis and jaundice, and a greater prevalence of extrarenal manifestations like

seizures, severe hypertension, pancreatitis, and gastrointestinal affectation. In addition, patients in the later era had higher anti-FH titers. In contrast, proteinuria, high creatinine and need for renal replacement therapy, severe anemia, thrombocytopenia, and low C3 levels and proteinuria were seen in both eras.

In the current study, the authors noted a similarly high prevalence of oliguria (82.4%) and extrarenal manifestations like seizures (36.8%), jaundice (26.3%), severe anemia (Hb of 5.6 ± 1.4 g/dL), and low C3. They also found that, as in prior studies,^{2,3} the disease was most commonly triggered by a febrile episode, a respiratory or diarrheal illness, and infections like COVID-19 could trigger relapses.⁵ They also found a higher incidence of pregnancy-associated HUS triggered by anti-factor antibodies than described previously.⁶

The time to renal remission (43 days) in this study was also longer than reported earlier, and this may have been a consequence of the less aggressive regimen of plasmapheresis or apheresis (PLEX) used in this study. This study identifies factors predicting unfavorable outcomes and lack of response to the existing treatment, namely increased age, female gender, presence of seizures, and higher anti-FH titers, which, as in earlier studies, predicted poorer response and risk of relapse.⁷ Although guidelines for plasma exchange in anti-FH antibody HUS have been published, there is a marked heterogeneity in treatment across the country, with less intensive regimens also showing excellent results.⁸ This study also used a less intensive plasma exchange regimen (minimum of five exchanges), which may explain the delayed renal response and nonresponsiveness in patients with higher titers (3455 vs 7557 AU/mL). A subset

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of patients may require more intensive treatment or the addition of other complement-blocking agents (currently unavailable in India). Such patients may have very high titers or an additional genetic component,⁹ for which this study does not have information. This subset needs more attention and should be the subject of further research in India. In earlier studies, anti-CFH titers > 8000 AU/mL accompanied by low C3 levels were associated with poor prognosis. In contrast, persistent or increasing titers > 2000 AU/mL after treatment and a cutoff of 1332 AU/mL six months after plasma exchange predicted relapses.^{2,6} In this study, although anti-CFH was associated with severe disease, also the response to plasma exchange and long-term remission was better in patients with antibody-positive disease. This difference, especially in terms of death and dialysis-free renal survival, was most marked between 6 and 12 months.

As antibody titers predict relapses, reliable titer monitoring is paramount in monitoring response and risk of relapse and adjusting immunosuppressive treatment or reinitiation of plasma exchange. This implies that a standardized and consistently reproducible assay should be widely available, ensuring that the sample collection and transport are correctly done [Box 1]. The first nationwide Indian study³ involved technology transfer from a reference laboratory in France to India. Its results also led to three European reference labs standardizing the assay and adopting one method that was the most accurate and reproducible.¹⁰ A commercial enzyme-linked immunosorbent assay (ELISA) was also evaluated against the reference method, and the limitations and recommendations regarding its use were outlined.¹⁰ As other laboratories in India adopted commercial ELISA kits, the discrepancies between the reference method and commercial ELISAs became evident, with one study using a commercial ELISA reporting markedly lower levels for the normal range in healthy controls and patients with disease.⁸

This study has some limitations. Being a single-center study of a rare disease, a matched control group could not be studied. Nevertheless, it advances our understanding of the disease, especially the long-term outcomes, the propensity to relapses, and the need for ongoing care, including monitoring for relapses and nonresponse. It also exposes the gaps in our understanding regarding nonresponsiveness to the current treatment and the areas needing further study, namely the need for a monitoring tool for antibody-negative disease over an extended period.

In conclusion, this study extends the spectrum of anti-FH antibody HUS, well described in Indian children to adults, with similar findings in terms of extrarenal manifestations, high titers, response to plasma exchange and immunosuppression, reasonable response rates and propensity for relapses to be triggered by second hits. It

Box 1: Best practices for diagnosis and management of HUS

When to suspect HUS?

HUS should be suspected in an unexplained AKI with thrombocytopenia, bearing in mind that this may also occur in infections like dengue, typhus, or leptospirosis. It may follow an uneventful antepartum course and normal delivery and the need to be distinguished from HELLP and TTP. In cases presenting late, a raised creatinine with disproportionate anemia, hypertension, and proteinuria should prompt a renal biopsy.

What complement assays should be done and how should they be interpreted?

Samples for anti-factor H antibodies, C3, C4, and ADAMTS 13 should be immediately drawn prior to commencing treatment with plasma exchange. Additional assays include CH50, AH50, and CD46 by flow cytometry and STX1 and 2 by PCR, which is important, although not a complement test. Genetic analysis is not required for initial treatment.

How should samples should be drawn and stored for complement assay?

Serum samples for anti-FH antibodies, CH50, and AH50 should be separated soon after the blood has clotted and centrifuged at 2000–3000 rpm for 15 minutes. Citrated or EDTA plasma, separated by centrifugation, is required for factor H, ADAMTS13, and C3 and C4 levels. All handling should be done on ice. Samples must be stored at –20°C and transported on ice if not processed within two hours to prevent in vitro consumption.

What are the treatment options?

Complement inhibition with agents like ecalizumab and ravalizumab are the recommended treatment for HUS, but are currently unavailable in India (they may become available by 2025). The high costs may be offset if they are included in the Government of India's Center for Excellence for Rare Diseases initiative.

Iptacopan, an oral factor B inhibitor, is currently in phase 3 trials in the United States, India, Taiwan, Japan, China, and Brazil (APPEL HUS).

Narsoplimab, a lectin pathway inhibitor, and Crovalimab are under trial, but India is not included at present.

The mainstay of treatment in India is plasma exchange using volume for volume replacement with fresh frozen plasma. For anti-factor H HUS, a combination with immunosuppression results in high remission rates and sustained benefits for over 24 months or more. The time appears right for a trial comparing less intensive plasma exchange and immunosuppression with the current standard of care.

also highlights the need for close monitoring, especially between 6 and 24 months, adequate supportive care, and the need therefore for the availability of a standardized antibody assay.

Conflicts of interest

There are no conflicts of interest.

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