Advances in Diagnosis and management of Atypical Hemolytic Uremic Syndrome

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Abstract:
The triad of microangiopathic hemolytic anemia, thrombocytopenia, and acute kidney injury is identified as hemolytic uremic syndrome (HUS). Complement activation is extremely active in HUS that is unusual. There have been reports of both hereditary and developed autoantibodies against the proteins that control complement. The lack of considerable mutation penetrance in all disease-causing genes demonstrates that a provoking event or trigger is necessary to disclose the complement regulatory failure. Prognosis is determined by the underlying genetic defect in both naturally occurring kidneys and kidneys that have undergone transplantation. Positive results from clinical trials using the complement inhibitor eculizumab to treat atypical HUS will impact how the condition develops.

Introduction

Atypical HUS, uncommon form of thrombotic microangiopathy (TMA), is characterized by diagnostic triad of acute kidney injury (AKI), thrombocytopenia, and microangiopathic hemolytic anemia (aHUS) (AP). **(1).**

Because the appraoch to aHUS is based on the clinical identification of TMAs., it might be challenging while also requiring the exclusion of all other causes of TMAs and HUSs. **(2).**

Complement regulatory protein (CRP) and genetic variants account for around 30% to 50% of cases of aHUS. No known identified mutation, accounting for 50% to 60% of all cases. Clinical manifestations of aHUS can also result from underlying causes such infections, malignancy, or pregnancy. These guidelines could alter when new information from aHUS patients is released. As important is the ability to recognize previously unknown mechanisms, causes, and symptoms early diagnosis and management of aHUS as is evaluating its etiology, causes, manifestations, and therapeutic choices. **(3).**

Epidemiology

Depending on how the disease is defined, the incidence statistics ranges from 0.23 to 0.42 cases per million people (or 0.1-0.11 cases per million people who are 16 to 17 years old). In children,

5–10% of instances of HUS are caused by atypical hemolytic uremic syndrome. 70% of children have their first episode before they turn 18 years old, and 25% experience it before the age of five of six months. Boys and girls have the same frequency **(4)**

Pathophysiology

The vast majority of patients have antibodies against proteins in the alternative complement pathway or mutations in the genes encoding the proteins. The complement system is made up of 3 paths: classical, lectin, and alternative. Because C3 hydrolyzes spontaneously, the alternate complement system is always active. The deposit of stimulated C3 on surface of cells initiates an amplification cycle. The result is the cleavage of C5 producing C5a (powerful anaphylatoxin) and C5b. **(5)**

A genetic complement defect that is inherited or acquired is prevalent in 50% to 70% of patients with aHUS. **(6)**

Gain in function mutations of effector factors or loss in function mutations of regulator factors are two attributes that can be seen in the complement genetic disorders. Various genes are observed in both complement-related and non-complement-related aHUS such as complement factor H (CFH) (20–30%), membrane cofactor protein (MCP or CD46) (10–15%), C3, complement factor I (CFI), complement factor B, THBD (encoding thrombomodulin), and diacylglycerol kinase epsilon. **(6)**

The CFHR1 and CFHR3 genes were deleted is closely associated with a hereditary propensity for the autoantibodies' suppression of CFH function. Moreover, some of these gene alterations have been seen in sepsis patients. **(7)**

Increased membrane attack complex formation results from increased C3b and C3 convertase synthesis caused by complement regulator factor dysfunction (C5b-C9). Endothelial injury brought on the membrane attack complex worsens vascular thrombotic lesions. Complement's prothrombotic effects are exacerbated by thrombomodulin genetic defects, which also lead to overexpression of Von Willebrand factor expression is down, and vascular endothelial growth factor is down. **(8)**

Regardless of the patient or one of their healthy parents having pathogenic mutations in complement genes, Complement-HUS is usually sporadic (85% of families). These results imply that rather than directly causing the disease, the patient's genetic background predisposes them to it. Uncertainty surrounds the causes of complement-insufficient HUS's penetrance. It has been hypothesised that illness risk is increased by combination Pathogenic mutations, which are present in 3% of patients, or haplotypes associated with risk (in membrane cofactor protein [MCP or CD46], complement factor H [CFH], and CFH-related protein) 1 [CFHR1]) **(7)**

Complement factor H (CFH)

Complement factor H (CFH) is a plasma protein that is primarily formed in the hepatocytes. Moreover, blood lymphocytes, monocytes, dendritic cells, and renal cells all create factor H "locally". (14) It is the primary regulator of the fluid phase of the complement's alternate route

(AP). It consists of 20 complement regulating protein modules (CCPs). The four N-terminal CCPs (CCPs 1-4) facilitate CFH regulator tasks by (1) fighting against FB for C3b binding, (2) speed up C3 convertase dissociation, and (3) serving as a mediator for factor I-facilitated proteolytic inactivation of C3b The C-terminal domains of CFH (CCP19–20) bind polyanions just like glycosaminoglycans to protect the host surface. The most frequent mutation in aHUS affects the regulation of cell-surface complement is impaired by the C-terminal region of CFH. (15) The genetic structure of On chromosome 1, the regulators of complement activation (RCA) gene cluster, which contains the gene CFH, is what leads to this mutational hotspot. The sequence similarity between CFH as well as five factor H-related proteins is extremely strong, despite the likelihood that the RCA cluster originated via multiple substantial chromosomal duplications. This similarity lends itself Nonallelic homologous recombination and microhomology-mediated end joining lead to gene conversions and genomic rearrangements (CFH/CFHR1 and CFH/CFHR3 hybrid genes). (16) A reverse CFHR1/CFH hybrid gene with the C-terminal CCPs of FHR has just been found 1 are switched out for the C-terminal CCPs of FH. This gene was created through nonallelic homologous recombination. This FHR1/FH hybrid protein functions like a competitive inhibitor of CFH in this situation rather than impairing CFH cell surface binding. (17) The most often mutated gene is Factor H (CFH), which was the first gene associated with aHUS. In aHUS patients, over 120 CFH mutations have been found (mutation frequency: 30%). Most frequently, these mutations lead to normal CFH levels, but they produce a protein that does not connect to or regulate complement on platelets and endothelial cells. (18) Linkage analysis was utilised by Warwicker et al. to pinpoint the risk zone in three aHUS families. The 26-cM area was discovered on chr1q32, the same The CFH and CFHR genes are housed in a gene cluster. Further CFH sequencing revealed a heterozygous c.3716C>G variation and a deletion c.145 148delAGAA in two of the three families. After that report, other investigations have discovered multiple additional CFH mutations linked to aHUS. (19).

Anti-CFH inhibitory antibodies have been found in 25% to 50% of paediatric cases and 5% to 10% of aHUS patients. These autoantibodies, like CFH genetic defects, preferentially target the C-terminus of complement, that leads to compromise the Complement regulation. The formation of CFH autoantibodies in aHUS is strongly linked to the homozygous loss of the CFHR1 and CFHR3 genes (20)

Triggers of aHUS:

As heterozygous mutations that predispose children to aHUS typically have limited penetrance, a trigger is frequently needed in order for the syndrome to obvious clinically. Systemic lupus erythematosus (15%), chemotherapy (16%, n = 28), and infection (63%, n = 92) were identified as the main causes of adult aHUS in a retrospective research (n = 147). The infection subgroup was dominated by bacterial infections, particularly upper respiratory tract infections, at 42% (n = 75). (21)

As there are unknown causes in more than one-third of all cases of aHUS, its erratic appearance, particularly in children, is even more puzzling. Nonetheless, research uncovering both established and new reasons is progressing quickly. (22) AHUS and COVID-19 are correlated, according to recent studies. It is believed that TMAs and the interalveolar endothelial cells of COVID-19 that are activated contribute to the etiological factors of aHUS. This connection could have cyclical patterns, and COVID-19 may play a role in the clinical presentation of aHUS in individuals who have overcome the virus.

Hepatitis B vaccination has also been linked to clinical symptoms of aHUS. Avci et al. reported a 55-day-old female infant who developed clinical manifestations of aHUS following receiving 10 ug of HBsAg and 0.475 mg of aluminium hydroxide. After receiving the vaccine twice, the patient experienced icteric sclera and jaundice. The first dosage was given without problem at delivery. Schistocytes and haemoglobin levels were decreased, while the concentrations of total bilirubin, LDH, C3, and creatinine were all abnormal. During a renal ultrasonography, her kidneys were discovered to be echogenic. In addition, the presence of diagnostic triad support the diagnosis of atypical HUS (26) In other case report, Two days after getting the hepatitis B vaccine, a patient had a triad of aHUS, according to Geerdink et al. These two reports show that there are correlation between vaccinated infant with hepatitis B vaccine and development of pediatric aHUS(3).

Clinical presentations

Atypical HUS is infrequently taken into account in the differential diagnosis, despite the fact that more prevalent conditions like sepsis can induce unexpected AKI, low level of platelet, and multiorgan failure in severely ill patients. Since DIC and sepsis, which occur more frequently in the pediatric intensive care unit, can mimic this condition, it is crucial for critical care doctors to recognise it. Some conditions with increased complement activation may also reveal it. Most importantly, this illness requires immediate attention and has a specialised therapy. (3) In more than half of the individuals with excessive alternative complement pathway activation, the disease may begin after trigger events (such as viral gastroenteritis, influenza, or immunisation). (4) Common symptoms include pallor, vomiting, tiredness, and edoema. The classical triad is present in the majority of cases. Other observations, however, might appear as the condition progresses. The cases that start off with normal platelet levels but then see a >25% decline from baseline should be kept an eye out for aHUS. While the kidney is the primary organ affected by aHUS, 20% of patients may also experience involvement of extrarenal systems, including as the brain, cardiovascular system, lungs, skin, retinal vascular system, and gastrointestinal tract(27). The most frequent extrarenal involvement, which affects 8 to 48% of patients, is brain involvement. (28) and Cardiovascular issues are common, Abdominal distention, and bloody diarrhea are observed in aHUS (27)

Diagnosis

STEC-HUS is the primary differential diagnosis for aHUS in children, but secondary HUS and ADAMTS13 deficiency TTP are more frequently seen in adults. (9) Blood samples should be quickly collected before to therapy in order to evaluate ADAMTS13 activity and distinguish between aHUS and TTP. (6) The test is usually beneficial for directing additional treatment and is often ready in a few hours. When test results are delayed, it may occasionally be essential to begin presumptive treatment (such as PEX) in individuals who are at high risk for TTP. About 40% of aHUS sufferers had C3 is low, and C4 is normal. However, because low levels of serum C3 have limited sensitivity and increased levels of serum C5a and soluble C5b-9 may not be specific enough to rule out complement aHUS. (30) All patients thought to have aHUS should submit to culture-based assays (serology or polymerase chain reaction; 30% of patients with complement-facilitated aHUS also experience simultaneous gastroenteritis, compared to 5% of STEC-HUS patients who do not experience prodromal diarrhea). (6) If SP-HUS is present, the Coombs should be done. Genetic testing is not helpful in an emergency. Excluding any other probable TMA etiology forms the foundation for the evaluation of aHUS.(7)

Treatment

Supportive treatment for aHUS focuses on managing acute renal damage and systemic consequences. When a patient has severe anemia, packed cells must be used. Except in cases of thrombocytopenia related to ongoing Platelet transfusions are only occasionally required in individuals with bleeding or those having invasive treatments. Fluid and electrolyte evaluation is critical for maintaining intravascular volume status and avoiding the effects of aHUS, acute kidney injury, and multisystem organ failure. Drugs that are nephrotoxic should be avoided, and electrolyte imbalances should be treated as a way. To manage hypertension, the appropriate drugs should be taken. individuals with uremia, excess fluid, or electrolyte problems require renal replacement treatment. Treatment options include plasma exchange and the complement inhibitor eculizumab **(31)**

Plasma exchange

Despite being the recommended treatment for aHUS, plasma exchange and plasma infusions (PEX/PI) do not deal with the root of complement insufficiency. PEX is a useful technique for providing acute care that facilitates the removal of proteins and antibodies. PEX/PI eradicates vWF multimers and autoantibodies in TTP patients while also restoring ADAMTS13 to normal. (31)

Treatment usually starts within 24 hours of the diagnosis and lasts for at least 5 days, or until the platelets are >100 000/cu mm and the schistocytes are 2% for 2 days, and then continuing twice per week. (31)

At each procedure, between 30 and 40 mL/kg (1 to 1.5 plasma volumes) of plasma are typically extracted and replenished with intravenous albumin solutions or fresh frozen plasma. (albumin 4.5% or 5%). Around 66% of an intravascular ingredient is removed by one plasma volume exchange, and 85% is removed by two. (32)

The ideal properties of molecules to be eliminated are: **(33)**

- High molecular mass (≥15 000 D).
- Slow formation pace.
- Minimal distribution volume; low turnover.

Plasma exchange has a number of negative impacts. It has been reported to result in Acute lung injury-related allergic, febrile, and Anaphylactic reactions to transfusion, transfusion-related circulatory overload, and infection are all possible outcomes. (34)

The underlying genetic alterations affect both the immediate and the long-term effects of PE/PI therapy on patients. In a previous study of 273 aHUS patients treated with PE/PI, it was discovered that nearly 70% had genetic changes passed either during the first episode or within three years of the disease's first presentation, or they developed a dependency on dialysis. (31)

Due to the insufficient recovery, experts in the vast majority do not recommomd to use (PEX/PI) therapy for initial treatment. for patients with aHUS. Special consideration is given to facilities that do not have immediate access to the complement inhibitor therapy eculizumab. PE should begin as soon as an aHUS diagnosis is made in these cases. If the patient does not achieve haematological remission despite 5-7 PE, has life-threatening symptoms (seizures, cardiac failure), PE complications, or vascular access, plasma therapy should be replaced with eculizumab it is available. The second instance concerns individuals who have anti-FH antibodies; in these cases, most specialists concur that PE and immunosuppression effectively lower circulating autoantibody levels and prevent their continued formation. (35)

Eculizumab is a humanised, IgG C5 recombinant antibody that prevents the division of C5 into C5a and C5b and the formation of membrane attack complexes (MAC). The activity of the alternative complement pathway is reduced as a result of its inhibitory effect, and prevents the complement system from performing proinflammatory, prothrombotic, and lytic tasks in addition to pro-inflammatory ones. According to animal research, the medication can pass through the placental barriers and harm or kill the foetus. The medicine has an 11 3 day half-life, and maintenance therapy is administered every two weeks. (4) A prospective research included aHUS patients who got eculizumab for their condition. All patients received eculizumab as opposed to continuing their plasma therapy. TMA activity ceased in the majority of patients (80–88%). As eculizumab treatment progressed, the majority of patients who were on dialysis were able to terminate their treatments because their eGFR increased. (4) Twenty-two children with aHUS received eculizumab for 26 weeks as part of a prospective research. By week 26, all patients had stopped receiving PE/PI, 18 had returned to hematologic normalcy, 16 had decreased their serum creatinine levels by 25% or more, and 14 had achieved complete TMA remission. Following these findings, Eculizumab is suggested as a drug of choice for the management of aHUS and shoud to begin immediately as a diagnosis of aHUS make (within 24 hours, if available), For critically ill patients with severe TMA who do not have access to eculizumab, PEX can be utilised and is frequently required while test results are being obtained. (7) Eculizumab prevents the terminal complement pathway from being activated. As a result, the patients would be vulnerable to infections caused by bacteria that have been capsuled, such as Neisseria meningitidis. Patients should ideally have their shots at least two weeks before starting

treatment. Nevertheless, the disease's quick onset makes this plan all but impossible. Antibiotics for prevention should be given in this scenario. Before beginning treatment with eculizumab, vaccinations Furthermore, protection against H. influenza type B and S. pneumoniae must be taken into account. allergies (24%), infections (24%), hypertension (5%), and chronic renal failure (5%) are among eculizumab's other serious side effects. There have also been reports of pyrexia, nausea, peripheral edoema, headache, diarrhoea, hypertension, stomach discomfort, vomiting, nasopharyngitis, and anaemia. The most frequent restriction on eculizumab use is the drug's exorbitant cost during therapy, which is more than $300 000 per year. As a result, research on stopping a course of therapy has grown in recent years. (37) In individuals who meet certain criteria, eculizumab withdrawal should be considered follows the normalisation or stabilisation of renal functions and at least 6 months of medication (or 3 months in MCP mutation patients). (38) Therapy duration is still debatable and subject to professional discretion. Upon finishing therapy for minimum 6 to 12 months, as well as at least 3 months of renal replacement therapy improvement, eculizumab therapy can be stopped in certain cases. (6)

Kidney transplantation

It should be postponed until at least six months after the initiation of dialysis and require remission of extrarenal symptoms due to the heterogeneity in results and disease recurrence rates, which can be accounted for by an underlying genetic defect (6)

The proteins that are produced in the liver CFH, CFB, and C3 are examples of the alternative complement route. Liver or combination For some aHUS patients, liver-kidney transplantation (CLKT) may be a viable treatment option. (35)

Prognosis

Atypical HUS is linked to unfavorable prognosis; approximately 50% of cases progress to end-stage renal disease, and up to 25% of individuals may be died during the acute stage of the syndrome. Adult patients were more likely than paediatric patients to progress to end-stage renal failure after the initial aHUS event. Various genetic defects can influence outcomes, therapeutic responsiveness, and the risk of post-kidney transplant relapse. CFH and CFI mutations have an extremely bad prognosis, with 80% of patients presenting with recurrent disease or relapse post kidney transplantation, in contrast to MCP mutations, which are often linked with good outcomes. (7)

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