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Editorial

Importance of Genetic Testing in the Diagnosis and Management of Atypical Hemolytic Uremic Syndrome

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Hemolytic anaemia, thrombocytopenia, and acute renal failure are the three components of hemolytic-uremic syndrome (HUS). Shiga toxin produced by *E. coli* is the main culprit (STEC HUS). The absence of STEC infection distinguishes atypical HUS (aHUS) from conventional HUS. A normal level of ADAMTS13 can also help distinguish it from thrombotic thrombocytopenic purpura (TTP). Atypical HUS can appear at any age, from infancy to adulthood. The cases with hereditary origins make for about 60% of aHUS. Even after full treatment, these people frequently experience relapse. In about 60% of these instances, end-stage renal failure develops (ESRD).

By locating a pathogenic mutation in one or more of the genes linked to aHUS, the diagnosis of genetic aHUS in a patient is established. The aHUS is often inherited either autosomal recessively by the presence of a pathogenic mutation in a single gene or autosomal dominantly with limited penetrance. Polygenic inheritance is uncommon. The reported mechanisms as of right now are as follows

- Heterozygous pathogenic mutation in at least one of the following genes: *C3, CD46, CFB, CFH, CFHR5, CFI, THBD,* and *VTN*.
- Homozygous or compound heterozygous pathogenic/likely pathogenic variants in DGKE.
- The following genetic modifiers, when present without one of the recognized molecular causes, increase the penetrance and severity of aHUS but may not actually cause the illness:
- *CFH-H3* haplotype [1]
- *CD46 (MCP)-GGAAC* haplotype [2]
- *CFHR3/CFHR1* homozygous deletion is linked to the development of anti-factor H autoantibodies, which results in autoimmune aHUS [3].

Single-gene tests, the use of a multigene panel, and thorough genomic testing are all molecular testing techniques for aHUS.

Individuals with aHUS who presented before the age of one year should undergo single gene testing, especially if there is consanguinity or proof of autosomal recessive inheritance. The first thing to think about is *DGKE* genetic screening. A multigene panel should be examined if *DGKE* screening fails to detect homozygous or compound heterozygous pathogenic variants.

Patients who presented with symptoms of aHUS after the age of one year should be tested using a multigene panel that contains the following genes: *C3, CD46, CFB, CFH, CFHR5, CFI, DGKE, THBD,* and *VTN.* A gene panel should be created to identify *CFH/CFHR1, CFHR1/CFH* hybrid alleles, and *CFHR1/CFHR4* deletions.

Testing for genetic modifiers like the *CFHR3/CFHR1* deletion, *CFH-H3,* and *CD46 (MCP)-GGAAC* haplotype should also be a part of molecular screening.[2,3] Environmental triggers (such as infection and pregnancy) and complement gene haplotypes, particularly homozygous *CFH-H3* and *CD46 (MCP)*-GGAAC, may increase the penetrance of aHUS [4]. Consideration may also be given to a multigene panel that contains other genes of relevance such *ADAMTS13, MMACHC, MTRR*, and *MTR.*

If single gene testing and/or multigene panel testing are unable to confirm a diagnosis in a patient with features of aHUS, comprehensive genetic testing techniques including whole exome sequenc-

ing, whole genome sequencing, and mitochondrial sequencing may be taken into consideration.

Genetic testing may help people with aHUS receive the most effective care

- **C3**: In aHUS patients with *C3* mutation, plasma exchange could remove mutated hyperactive C3 and also offer regulatory plasma proteins to offset complement activation caused by aberrant C3.
- **CFB:** There is a lack of information on how plasma exchange treatment affects those who have *CFB* pathogenic mutations. Plasma exchange has been shown to induce remission [5].
- **CD46**: According to earlier research, the majority of aHUS patients (80%-90%) experience remission after receiving plasma exchange therapy [6,7]; however, full recovery from the acute episode was also shown in 100% of individuals who weren't given plasma treatment [8]. The clinical severity of the acute episode should be taken into consideration when deciding whether to administer plasma exchange therapy to the patient.
- **CFH**: The use of plasma exchange in aHUS patients with *CFH* pathogenic mutations has been justified by the idea that normal CFH will make up for the genetic shortcoming. According to earlier research, several patients with *CFH* pathogenic mutations did not benefit from plasma therapy; instead, they acquired end-stage renal disease and passed away. Others, however, needed weekly plasma exchanges to raise the plasma levels of CFH and achieve remission [9].
- **CFI**: According to earlier research, more plasma is needed to produce enough normal CFH or CFI to make up for the genetic shortcoming.[7] Only 25% of cases with harmful *CFI* mutations who underwent plasma exchange therapy experienced remission [8].
- **DGKE**: Data linking DGKE deficiency to the complement cascade are lacking, although relapses have been observed in aHUS patients who had plasma therapy, suggesting that this therapy may not be helpful for patients with *DGKE* pathogenic mutations [10].
- **THBD:** About 80% of patients with *THBD* pathogenic mutations experienced illness remission after plasma exchange [8].

The significance of genetic testing is emphasized in this article since it is essential for making a precise diagnosis and starting the appropriate treatment in aHUS patients.

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