Atypical HUS Facts - 2023 SEPT 2024

– Atypical Hemolytic Uremic Syndrome –

Atypical HUS: A Very Rare Disease

Atypical HUS is a rare type of thrombotic microangiopathy (TMA), a life-threatening disease where tiny blood clots cause damage to organs such as the kidneys, heart, lungs & brain.

Atypical hemolytic uremic syndrome is currently known by multiple names and classified by various means. Information and research may be tagged by terms such as complement disease, primary TMA, or phrases related to suspected triggers, such as pregnancy-associated HUS.

Only a handful of people per million have aHUS. Exact patient numbers vary by nation, and whether new aHUS cases (incidence) or total current patients with this diagnosis (prevalence) are considered.

aHUS can cause uncontrolled activation of the complement system, part of the body's natural immune system, where the lining of small blood vessels shears apart red blood cells (RBC). Tiny clot formation, with its reduction in RBCs and platelet counts, clog blood flow and impair organ function.

People can experience aHUS at any age, for varied durations and with great range in severity. It can become a chronic disease state or aHUS activity may suddenly, unpredictably flaring into an acute and serious medical event. Affecting all areas of life for patients and their family, aHUS can impact their quality of life, stress levels, and mental wellness.

aHUS Diagnosis & Effects

Atypical HUS is difficult to tell apart from conditions with similar conditions, and there is no single test to diagnose aHUS. Instead, aHUS remains a 'diagnosis of exclusion' or what condition is left after other illnesses are ruled out.

Symptoms of aHUS are not often visible and usually present with few and vague signs, such as fatigue or nausea, or perhaps confusion or unexplained skin bruising. This lack of clear, clinical signs may lead to difficulty in receiving a rapid and accurate diagnosis to obtain appropriate medical care.

Clinical determination among diagnostic pathways (TMA algorithms) is supported through specialized lab tests such as rapid ADAMTS13 and complement levels as well as traditional blood testing such as complete blood counts and metabolic panels.

aHUS Genetics: *aHUS is mainly due to abnormalities in complement regulatory genes, which can be dormant in family members as healthy carriers whose offspring inherit genetic predisposition for aHUS. Genetic screening results may be inconclusive. It is unpredictable if or when their offspring may experience aHUS activity, or to what degree. (Ardissino et al, 2021)*

Multidisciplinary Care Teams — *Care for aHUS patients is most often headed by a physician specializing in hematology (blood) or nephrology (kidneys) but the function of any organ or body system can be damaged. Complications involving the central nervous system may include risk of seizure or stroke, or may negatively impact the patient's cognitive functioning in terms of confusion, focus or memory issues.*

Facts: A Deep Dive into Atypical HUS

HUS Basics — *Atypical HUS received its vague name to distinguish a subset of patients apart from the more common HUS, such illness as caused by Shiga toxin–producing Escherichia coli (STEC) infection. (Jokiranta TS, 2017) Currently HUS is generally divided into infectious, secondary, or atypical disease groups. (Yerigeri et al, 2023) Fewer than 10% of HUS cases are attributed to atypical HUS. (Loirat C, Frémeaux-Bacchi V, 2011)*

Genetic causes of aHUS accounts for an estimated 60% of all aHUS cases. Variants associated with genetic aHUS include C3, CD46 (MCP), CFB, CFH, CFHR1, CFHR3, CFHR4, CFHR5, CFI, DGKE, THBD, and VTN. (Noris, M, Bresin, E, Mele C, Remuzzi G. (GeneReviews® ed. 2021) The most frequent mutations seen in aHUS are heterozygous and affect Factor H, involved in 21–25% of cases. (Feitz W, van de Kar N, Orth-Höller D, van den Heuvel L, Licht C. 2018)

Kidneys are the organs primarily damaged by aHUS, with only about 20% of patients having preserved kidney function at diagnosis, but it can cause negative impacts throughout the body. (De Yao J, Kaplan B, Magro C. 2015). Atypical HUS may present as severe hypertension (high blood pressure) without hemolysis (destruction of red blood cells) or thrombocytopenia (low platelet count). (Tsai HM, 2016)

— continued on page 2

Facts: A Deep Dive into Atypical HUS — *continued from page 1*

Extra-Renal Manifestations — *People with aHUS have impaired kidney function, with rates which vary based on the causative mutation, resulting in about 50% of patients progressing to end-stage renal disease (ESRD) requiring chronic dialysis. Up to 43% of aHUS cases exhibit cardiovascular symptoms (such as myocardial infarction, hypertension, peripheral gangrene),*

Up to 48% may have central nervous system involvement (such as confusion, stroke, seizure), 46% may have pulmonary issues (such as pulmonary edema and/or hemorrhage, or dyspnea/breathing difficulty), while 37% can experience gastrointestinal issues (such as nausea, pancreatitis, abdominal pain). (Yerigeri K, Kadatane S, Mongan K, Boyer O, Burke LG, Sethi SK, Licht C, Raina R. 2023)

Learn MORE at the aHUS Alliance Info Centre

Noris M, Bresin E, Mele C, et al. Genetic Atypical Hemolytic-Uremic Syndrome. GeneReviews® [2021 Sep 23].

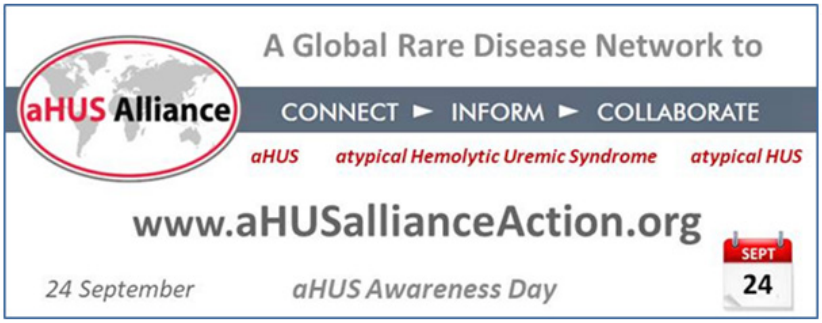
Atypical HUS Research: Listed by Categories: Diagnosis, Treatment, Pregnancy, TMA, Genetics, more

Resource Page & Article Index: Clinical Network & Study Centers, Patient Groups, Issue Specific Topics

Know aHUS: Know Us: A Print & Share pdf on aHUS facts & issues, Available in 3 languages: ENG, FR, ES

Patient Surveillance — *During initial onset of aHUS, or during recurring episodes, blood samples can determine levels and blood cell counts for: platelets, hematocrit and hemoglobin, creatinine, BUN (blood urea nitrogen) and haptoglobin levels. Specialized testing such as ADAMTS13 and complement levels can provide important information (National aHUS Service, UK website). A genetic renal panel may provide test results which provide insights into personalized methods of treatment, to include prognosis and recurrence risk for aHUS. (Bu et al, 2016) More consensus is needed regarding patient monitoring, to include home monitoring like monthly blood pressure checks and home urinalysis strip testing, with increased frequency when feeling unwell. Some clinicians may order a check of these aspects every month in the the first year after an aHUS episode, then every three to six months in the following years: serum concentration of hemoglobin, platelet count, and serum concentrations of creatinine, LDH, C3, C4, and haptoglobin. (Noris et al. GeneReviews® 2021)*

Treatment Options — *Advancements in understanding the disease have led to better outcomes for both adult and pediatric aHUS patients (Nester et al, 2015). Treatment duration with complement inhibitors such as eculizumab and ravulizumab has moved away from all aHUS patients needing a lifelong C5 blockade to a more individual approach to long-term disease management. (Fakhouri F, Schwotzer N, Frémeaux-Bacchi V. 2023) & (Bouwmeester RN, Duineveld C, Wijnsma KL and CUREiHUS Study team. 2022) Clinical trials and/or drug approval processes are underway for patients with aHUS or similar conditions such as TMAs or PNH, among them are: Roche's crovalimab, Novartis' iptacopan or biosimilars such as Amgen's Bekemv™ (ABP 959) and Samsung Bioepis' Epysqli™ (SB12). Patient preferences tend toward less disruption to daily life, overall improvement in 'quality of life' measures, and better life/treatment balance. (Mauch et al, 2023). FMI: https://bit.ly/aHUS2022drugReview*



Treatment Limitations — *Plasma infusion or exchange is still utilized, particularly where complement inhibitors are not available, but plasma resistance or plasma dependence is possible. Complement inhibitors have been used for aHUS patients with mutations in CFH, C3, CFB, and CFI, but DGKE mutations are not associated with activation of the complement pathway and may require a different therapeutic approach. (Noris et al. GeneReviews® 2021) Drug cost often drives drug access and national policy, with consideration of treatment-cost balance for small patient populations common for rare diseases like aHUS.*