Atypical HUS Facts: 2024 SEPT 2025

• *Atypical Hemolytic Uremic Syndrome* •

Atypical Hemolytic Uremic Syndrome (aHUS) is a rare genetic disorder that primarily affects the kidneys but can also have devastating impact on other organs. It is characterized by the formation of blood clots in small blood vessels, leading to destruction of red blood cells (hemolytic anemia), low platelet count (thrombocytopenia), and acute kidney damage. The condition is often triggered by an abnormal activation of the complement system, a part of the immune system, due to genetic mutations.

Occurring in an estimated 2 to 9 people per million, the rarity of aHUS contributes to the challenges in diagnosing and treating the condition. Symptoms can mimic other, more common diseases, leading to misdiagnosis and delays in appropriate treatment. Since timely intervention is critical for improving aHUS patient outcomes, it is essential to work toward bridging knowledge gaps and raising awareness about the disease, to ensure that patients receive accurate and rapid diagnosis to start them on an appropriate pathway to care. (aHUS Alliance Global Action: LW)

Symptoms at onset may be vague and attributed to other causes. Most common are: fatigue, skin bruises or paleness, nausea/vomiting, abdominal pain, shortness of breath, or discolored/decreased urine output. (Formeck and Swiatecka-Urban, 2019)

Diagnosis is challenging. Currently there's no universally accepted diagnostic criteria (Fakhouri F, 2023), instead other conditions are ruled out to leave aHUS as a 'diagnosis of exclusion'. Tests: With no single definitive test for aHUS, physicians may base their diagnosis on: blood tests, urinalysis, ADAMTS13 levels, kidney function assessments, genetic testing, biomarker studies, and complement system analysis.

Genetic Factors Genetic predisposition for aHUS can run in families, with mutations in various complement regulatory genes such as CFH, MCP, and CFI. (Noris, M and Goodship, THJ et al, 2009). Around 10-25% of aHUS cases may be linked to inherited genetic mutations, but the majority of aHUS cases occur sporadically: randomly or infrequently, without a clear pattern of inheritance or environmental cause (Kavanagh D et al, 2013). Genetic dysregulation of the alternative complement pathway is identified in 40-60% of patients with aHUS (Spasiano, 2023).

Triggers for atypical HUS activity are varied, and often involve factors that cause abnormal activation of the complement system (Brocklebank et al, 2023). In addition to genetic predisposition, certain environmental factors can trigger or worsen aHUS such as viral or bacterial infections, pregnancy (Rondeau, 2022), some vaccines (Moradiya et al, 2024), or certain medications like immunosuppressants or chemotherapy agents which may provoke an immune response. Genetic predisposition for aHUS has been studied among family members of patients (Ardissino et al, 2021). Sometimes underlying medical conditions may trigger aHUS activity (Licht et al, 2024), such as certain autoimmune diseases or cancers which impact the immune system or produce substances that activate the complement cascade.

Treatment with a complement inhibitor can be effective for patients falling within the two-thirds classified as complement-mediated aHUS (Shaefer, 2018); as identifiable genetic abnormalities or autoantibodies related to the complement system, cmTMA. Treatment differs for patients whose mutations lie within genes involved in the coagulation pathway, such as DGKE (Westra et al 2016), as well as for autoimmune diseases or secondary forms of aHUS that can be independent of direct complement involvement. Drugs are currently in development to address varied aHUS/TMA clinical needs, and feasible goals for lower cost alternatives to current therapies so more nations can afford access to appropriate treatments.

aHUS Affects more than Physical Health

'Rise above aHUS'

"Kidney diseases involving complement overactivation can have a profound impact on the daily lives of patients and caregivers, limiting participation in important or meaningful activities." and "For young patients, the lack of natural history data leads to uncertainty regarding course and impact of disease, which can influence decisions on career and family planning" (Vivarelli et al. 2024, KDIGO)

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Atypical HUS: Its Far-Reaching Impact Multi-Organ Involvement

Kidneys: Damage occurs at varied levels for all aHUS patients, but severity ranges widely and differs from functional injury to renal failure. Atypical HUS activity has potential to affect multiple organs simultaneously. (Raina et al, 2019)

Central Nervous System (CNS)/ Brain: Occuring in up to 20-40% of cases with symptoms such as seizures, confusion, stroke, and other neurological impairments, patients may experience mild to more serious issues resulting in memory or cognitive difficulties.

Cardiovascular System: Blood vessel linings are affected with aHUS activity and, together with decline in kidney function, creates high blood pressure (hypertension) in most patients. In approximately 10-20% of cases serious heart complications such myocardial infarction, blood flow issues (ischemia) or heart failure may occur.

Impact at Home - Work - School

- Atypical HUS can occur as a chronic illness or as irregular episodes of aHUS activity which vary in severity, duration, and organs affected.
- Social impact and economic burden can affect all areas of life for aHUS patients, family members, and caregivers such as mental health, daily routines, relationship issues, lifestyle impact on the family, and more. (Bouwmeester, 2024)
- People with aHUS can experience unpredictable and rapid changes in their physical health with few warning signs. Modifications may be needed to accommodate unexpected medical care, changes to short/long term memory, variable task completion rate, or inability to focus due to anemia or poor kidney function.

Gastrointestinal Tract: GI issues occur in about 20-25% of cases and may include symptoms like abdominal pain, nausea, vomiting, diarrhea, or more rare and severe complications such as pancreatitis. (Yerigeri, 2023)

Pulmonary Involvement / Lungs: Seen in about 5-10% of cases, respiratory problems may occur and may include pulmonary hypertension, respiratory distress, and sometimes pulmonary hemorrhage.

Liver, Eyes, Skin: Although less frequently affected, liver involvement can occur (checked by ALT or AST tests); visual disturbances/ vision loss may arise; or skin issues appear (lesions, signs of jaundice, or irregularities like petechiae).

Taming aHUS: Complement & Thrombotic Microangiopathy

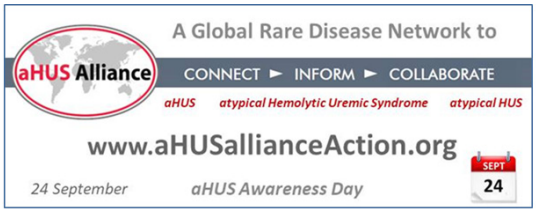
Advancements in medicine have evolved to position 'atypical HUS' diagnosis as a grouped spectrum of conditions that are similar but different in key aspects, which currently hinders how rapidly clinicians can diagnose and effectively treat patients.

The *complement system* is a series of proteins that activate as a cascade to destroy causes of disease, reduce inflammation, and help healing (as part of the immune system). Atypical HUS is one type (syndrome) of *thrombotic microangiopathy* or *TMA*, which shares similar features: destruction of red blood cells and platelets as microclots form within small blood vessels. If the patient's complement system is excessively active (even when it shouldn't be) that can lead to excessive inflammation and tissue damage. But if aHUS is caused by key components of the complement system being deficient or missing, a major factor is the reduced ability to clear pathogens.

Treatment. Therapeutic Drugs. Disease Management. Relapse Risks. These are different for aHUS patients depending on complement involvement and genetics. Clearly identifying aHUS sub-types and causes (etiology) will yield better patient outcomes.

Nester C et al. *An Expert Discussion on aHUS Nomenclature: Identifying a road map to Precision* (NKF) doi: 10.1016/j.kint.2024.05.021

Vivarelli M et al. *The role of complement in kidney disease:* (KDIGO) Controversies Conference. 2024 Sep doi: 10.1016/j.kint.2024.05.015



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