Clinical and genetic predictors of atypical hemolytic uremic syndrome phenotype and outcome

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Atypical hemolytic uremic syndrome (aHUS) is a rare, genetic, life-threatening disease. The Global aHUS Registry collects real-world data on the natural history of the disease. Here we characterize end-stage renal disease (ESRD)-free survival, the rate of thrombotic microangiopathy, organ involvement and the genetic background of 851 patients in the registry, prior to eculizumab treatment. A sex-specific difference was apparent according to age at initial disease onset as the ratio of males to females was 1.3:1 for childhood presentation and 1:2 for adult presentation. Complement Factor I and Membrane Cofactor Protein mutations were more common in patients with initial presentation as adults and children, respectively. Initial presentation in childhood significantly predicted ESRD risk (adjusted hazard ratio 0.55 [95% confidence interval 0.41–0.73], whereas sex, race, family history of aHUS, and time from initial presentation to diagnosis, did not. Patients with a Complement Factor H mutation had reduced ESRD-free survival, whereas Membrane Cofactor Protein mutation was associated with longer ESRD-free survival. Additionally extrarenal organ manifestations occur in 19%–38% of patients within six months of initial disease presentation (dependent on organ). Thus, our real-world results provide novel insights regarding phenotypic variables and genotypes on the clinical manifestation and progression of aHUS.

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Atypical hemolytic uremic syndrome (aHUS) is a rare disease that is complex to diagnose because of its heterogeneity. All forms of HUS are characterized by thrombotic microangiopathy (TMA) and are defined by the triad of nonimmune microangiopathic hemolytic anemia, thrombocytopenia, and vital organ damage, most commonly affecting the kidney.[1–3] In at least 50% of patients, aHUS is the consequence of genetic or autoimmune abnormalities leading to dysregulation of the alternative complement pathway on the surface of the vascular endothelium.[1–4] Prior to the availability of effective treatment, disease outcomes were poor and could be life-threatening. In a previous report, 29% and 56% of children and adults with aHUS, respectively, progressed to end-stage renal disease (ESRD) or death within 1 year of disease presentation. At 5 years, the proportions were 36% and 64%, respectively.[5] Recommendations for disease management involved frequent plasma exchange or infusion.[6] More recently, eculizumab, a humanized monoclonal antibody, has been shown to be effective in treating patients with aHUS.[7–10] These studies led to regulatory approval of eculizumab for the treatment of patients with aHUS in several regions and countries since 2011.

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aHUS is an ultra-rare disease with a reported incidence of approximately 0.5 per million per year,[11] limiting the number of patients available to power clinical trials. Therefore, international patient registries are a key strategy for improving knowledge of the natural history of the disease, evaluating the effectiveness of clinical therapies, monitoring drug safety, and measuring quality of care in a real-life setting.[12,13] The Global aHUS Registry was established to assess the natural history of aHUS irrespective of management choice or presence of potential precipitating factors.

The Global aHUS Registry is the largest collection of demographic, clinical, and genetic information from patients suffering from this ultra-rare disease. The methodology, pattern of global participation, and basic demographics of patients enrolled by November 30, 2015 have been reported.[14] The objective of the present study was to characterize ESRD-free survival, TMA rate, organ involvement, and genetic background of the patients enrolled in the Global aHUS Registry, prior to eculizumab use.

RESULTS

Patient demographics and clinical characteristics

In total, 851 patients were included in this analysis. Table 1 summarizes demographic characteristics at study entry, among pediatric ($n = 387$; 45%) and adult ($n = 464$; 55%) patients (categorized by age at initial presentation). A family history of aHUS was reported by 133 patients (16%) (73% of whom had affected first-degree relatives only, 12% second-degree relatives only, and 15% both first- and second-degree relatives). Initial disease presentation was often recent, occurring after 2011 in 38% of pediatric patients ($n = 195$) and 62% of adult patients ($n = 318$). Plasma exchange or infusion was more commonly used for adult than for pediatric patients with aHUS ($P < 0.0001$). Patient data were censored at time of eculizumab initiation and patient disposition for the analyses described herein are shown in Supplementary Figure S1.

Complement abnormalities and anti-CFH antibodies

Of patients with ≥5 genes tested, 119 (45%) had a mutation in ≥1 aHUS-associated gene or anti–complement factor H (CFH) antibody (Table 2). Patients presenting in childhood were significantly more likely to have membrane cofactor protein (MCP) mutations ($P = 0.0009$) and less likely to have complement factor I (CFI) mutations ($P = 0.0036$) than were patients with aHUS presentation in adulthood. The rarest mutation was in complement factor B (CFB), whereas anti-CFH antibodies were common in both pediatric and adult patients. In addition to complement abnormalities, diacylglycerol kinase ε (DGKε) mutations were observed in 8% of the 101 patients tested (all with initial presentation during childhood). The location of genetic mutations is shown in Supplementary Figure S2 and the characterization of genetic changes are summarized in Supplementary Table S1. Country-specific genetic screening patterns demonstrated there was no potential bias from unequal gene coverage between individual countries (Supplementary Table S2).

Table 1 | Patient demographics and clinical characteristics

Characteristic	All ($n = 851$)	Initial presentation in childhood ($n = 387$)	Initial presentation in adulthood ($n = 464$)
Age at initial disease presentation, yr[a]	21.4 (4.4–37.2)	3.8 (1.0–7.7)	35.4 (26.8–51.0)
Age at study entry, yr[b]	25.7 (10.2–43.1)	8.8 (4.5–14.8)	41.2 (30.9–53.9)
Race			
Caucasian	734 (86)	313 (81)	421 (91)
Black	37 (4)	14 (4)	23 (5)
Asian	18 (2)	12 (3)	6 (1)
Other	62 (7)	48 (12)	14 (3)
Female	468 (55)	166 (43)	302 (65)
Family history of aHUS	133 (16)	75 (20)	58 (13)
Duration from initial disease presentation to enrollment, yr	1.7 (0.3–6.6)	3.1 (0.7–8.9)	1.2 (0.2–5.2)
Patients with initial disease presentation within 6 mo prior to study entry	392 (46)	149 (39)	243 (52)
PE/PI prior to study entry	484 (57)	198 (51)	286 (62)
Duration of PE/PI treatment, mo	0.6 (0.1–2.0)	1.0 (0.2–4.8)	0.4 (0.1–1.4)
Dialysis prior to study entry	473 (56)	201 (52)	272 (59)
Chronic dialysis (duration longer than 3 mo)	209 (25)	82 (21)	127 (27)
Patients with ESRD prior to study entry or ESRD developed up to data cut[c,d]	219 (27)	90 (24)	129 (30)
Number of kidney transplants			
1	126 (15)	42 (11)	84 (18)
≥ 2	34 (4)	16 (4)	18 (4)

aHUS, atypical hemolytic uremic syndrome; ESRD, end-stage renal disease; PE/PI, plasma exchange or infusion.
Values are median (interquartile range) or *n* (%).
[a]Patients were categorized by age at initial aHUS presentation: pediatric (<18 years old) or adult (≥18 years old).
[b]Study entry was defined as follows: at enrollment for patients never treated with eculizumab or prior to eculizumab treatment initiation for patients who had ever received eculizumab.
[c]Data from $n = 808$ patients included in the time to ESRD analyses (see Supplementary Figure S1); ESRD was defined as a report of chronic dialysis (dialysis lasting ≥3 months) or kidney transplant.
[d]Where patients had multiple transplants and ESRD only 1 event was counted.