Clinical Characteristics and Outcome of Canadian Patients Diagnosed With Atypical Hemolytic Uremic Syndrome

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Abstract

Background: Atypical hemolytic uremic syndrome (aHUS) is an extremely rare, heterogeneous disease of uncontrolled activation of the alternative complement pathway that is difficult to diagnose. We have evaluated the Canadian patients enrolled in the Global aHUS Registry to provide a Canadian perspective regarding the diagnosis and management of aHUS and the specific challenges faced.

Objective: To evaluate Canadian patients enrolled in the Global aHUS Registry to provide a Canadian perspective regarding the diagnosis and management of aHUS and the specific challenges faced.

Methods: The Global aHUS Registry is an observational, noninterventional, multicenter study that has prospectively and retrospectively collected data from patients of all ages with an investigator-made clinical diagnosis of aHUS, irrespective of treatment. Patients of all ages with a clinical diagnosis of aHUS were eligible and invited for enrollment, and those with evidence of Shiga toxin–producing Escherichia coli infection, or with ADAMTS13 activity ≤10%, or a subsequent diagnosis of thrombotic thrombocytopenic purpura were excluded. Data were collected at enrollment and every 6 months thereafter and were analyzed descriptively for categorical and continuous variables. End-stage renal disease (ESRD)-free survival was evaluated using Kaplan-Meier estimates, and ESRD-associated risk factors of interest were assessed using Cox proportional hazards regression models. Patients were censored at start of eculizumab for any outcome measures.

Results: A total of 37 Canadian patients were enrolled (15 pediatric and 22 adult patients) between February 2014 and May 2017; the median age at initial aHUS presentation was 25.9 (interquartile range = 6.7-51.7) years; 62.2% were female and 94.6% had no family history of aHUS. Over three-quarters of patients (78.4%) had no conclusive genetic or anti-complement factor H (CFH) antibody information available, and most patients (94%) had no reported precipitating factors prior to aHUS diagnosis. Nine patients (8 adults and 1 child) experienced ESRD prior to the study. After initial presentation, there appears to be a trend that children are less likely to experience ESRD than adults, with 5-year ESRD-free survival of 93 and 56% (P = .05) in children and adults, respectively. Enrolling physicians reported renal manifestations in all patients at initial presentation, and 68.4% of patients during the chronic phase (study entry ≥6 months after initial presentation). Likewise, extrarenal manifestations also occurred in more patients during the initial presenting phase than the chronic phase, particularly for gastrointestinal (61.1% vs 15.8%) and central nervous system sites (38.9% vs 5.3%). Fewer children than adults experienced gastrointestinal manifestations (50.0% vs 70.0%), but more children than adults experienced pulmonary manifestations (37.5% vs 10.0%).

Conclusions: This evaluation provides insight into the diagnosis and management of aHUS in Canadian patients and the challenges faced. More genetic or anti-CFH antibody testing is needed to improve the diagnosis of aHUS, and the management of children and adults needs to consider several factors such as the risk of progression to ESRD is based on age (more likely in adults), and that the location of extrarenal manifestations differs in children and adults.

Abrégé

Contexte: Le syndrome hémolytique et urémique atypique (SHUa) se caractérise par l’activation incontrôlée de la voie alternative du complément. Il s’agit d’une maladie rare, hétérogène et très difficile à diagnostiquer. Nous avons évalué les patients Canadiens inscrits au registre international du SHUa afin d’offrir une perspective canadienne sur le diagnostic et la prise en charge du SHUa, de même que sur les défis posés par la maladie.

Objectif: Évaluer les patients Canadiens inscrits au registre international du SHUa afin d’offrir une perspective canadienne sur le diagnostic et la prise en charge du SHUa, de même que sur les défis posés par la maladie.

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What was known before

Atypical hemolytic uremic syndrome (aHUS) is difficult to diagnose and historically, prognosis (eg, end-stage renal disease [ESRD] or death) has been poor. Globally, ESRD or death appears to be related to whether aHUS occurred in adulthood or childhood, with ESRD more likely in adults and mortality higher in children.

What this adds

To improve the diagnosis of aHUS in Canada, more genetic or anti-CFH antibody testing is needed. We present the Canadian perspective regarding the diagnosis and management of aHUS compared with the global observation: the management of Canadian children and adults needs to consider several factors; for example, age impacts the risk of...
progression to end-stage renal disease (it is more likely in adults), and extrarenal manifestations affect different organ systems in children and adults.

Introduction

Atypical hemolytic uremic syndrome (aHUS) is extremely rare, with reported incidence rates of 0.75 to 2.0 cases per million people. A heterogeneous disease of uncontrolled activation of the complement system, aHUS is difficult to diagnose; it can be defined as thrombotic microangiopathy (TMA), characterized by nonimmune microangiopathic hemolytic anemia, thrombocytopenia, and organ damage, after exclusion of discrete forms of HUS and thrombotic thrombocytopenic purpura (TTP). All forms of HUS involve the kidneys. Historically, the prognosis of aHUS has been poor, with rates of death or end-stage renal disease (ESRD) between <20% and 80% depending on the specific mutation (or presence of anti-complement factor H [CFH] antibodies) causing HUS. End-stage renal disease or death tends to be related to whether aHUS occurred in adulthood or childhood; adults were more likely to progress to ESRD after the first aHUS episode, whereas children showed higher mortality than adults. However, in 2011, the treatment of aHUS changed following the approval of eculizumab, a monoclonal antibody that binds to C5 and inhibits activation of the terminal complement pathway. Eculizumab is now recommended as first-line treatment for aHUS following diagnosis, based on pivotal trial data showing the efficacy and safety of eculizumab in children and adults with aHUS.

Initiated in 2012, the Global aHUS Registry (an observational, noninterventional, multicenter study) has prospectively and retrospectively collected data from patients of all ages with an investigator-made clinical diagnosis of aHUS, irrespective of treatment. Recent data from 851 patients enrolled in the Global aHUS Registry, who were censored from the analysis at the time they received eculizumab, identified a sex-specific difference according to the age at initial disease onset, with the male:female ratio for children being 1.3:1, whereas for adults it was 1:2. In addition, mutations in the genes encoding membrane cofactor protein and complement factor I were more common in children and adults, respectively. In this study, ESRD as an outcome was related to age at initial presentation of aHUS: presentation in childhood predicted a lower risk of ESRD compared with first presentation in adulthood (adjusted hazard ratio [HR] = 0.55 [95% confidence interval [CI] = 0.41-0.73]). Extrarenal organ manifestations were found to occur within 6 months of initial disease presentation (dependent on organ) in 19% to 38% of patients.

Using the maximum estimated incidence rate of 2 cases per million, and based on a Canadian population of approximately 37 million, there are potentially 74 patients with aHUS in Canada. It is therefore not surprising that data on aHUS in Canadian patients have been limited to case study reports. We have taken the opportunity to analyze hitherto the largest group of aHUS patients in Canada and to describe the challenges faced in the diagnosis and management of Canadian patients with aHUS during a recent period (2015-2017) using data from the Global aHUS Registry.

Methods

Study Design

The details and objectives of the Global aHUS Registry (NCT01522183) have been reported previously. The industry-sponsored Registry also fulfills postmarketing regulatory requirements to provide long-term follow-up on patients treated with eculizumab. Briefly, patients of all ages with a clinical diagnosis of aHUS made at the discretion of enrolling physicians, irrespective of treatment, were eligible and invited for enrollment. There was no requirement to have an identified complement gene abnormality or CFH autoantibody, nor were patients required to have previous or ongoing treatment with eculizumab. Patients were excluded if there was missing consent, or if there was evidence of Shiga toxin–producing Escherichia coli infection, or with decreased ADAMTS13 activity to <10%, or a subsequent diagnosis of TTP. Adults and parents/guardians of children provided written informed consent, as deemed appropriate by research ethics boards and/or independent ethics committees.

Data Collection

At enrollment and every 6 months thereafter, the following data were collected where available: patient demographics, medical and disease history (including potential precipitating factors such as prior kidney transplantation, malignancy, pregnancy, autoimmune disease, and malignant hypertension), symptomatology, investigator-reported TMA complications, targeted laboratory results (including genetic tests), associated treatments and concomitant medications, clinical and patient-reported outcomes, safety evaluations, adverse events, and other information regarding treatment or disease management.

Data cutoff for this analysis of Canadian patients was May 5, 2017, with those patients having data for birth date, sex, date of initial aHUS presentation, and Registry enrollment date included in the analysis, prior to eculizumab treatment. Pediatric and adult patients were defined as those being <18 and ≥18 years of age at initial disease presentation. For the assessment of TMA rate, only patients diagnosed between 2006 and 2011 with ≥6 months of follow-up were included (this avoided potential treatment differences following the approval of eculizumab and inflating the measured rate due to a short follow-up time). Collection of data regarding extrarenal organ manifestations related to aHUS was limited to patients diagnosed with aHUS after 2011, to reduce recollection bias. While the investigators reported
extrarenal manifestations as related to aHUS, it is unclear whether they were the trigger or consequence of the TMA.

### Statistical Analysis

Descriptive statistics, proportions for categorical variables, and median and interquartile ranges (IQRs) for continuous variables were used to describe the demographic and clinical characteristics of the overall pediatric and adult patient populations (including age at initial presentation, sex, family history of aHUS [defined as patients with at least 1 family member with aHUS], time from initial disease presentation to diagnosis, plasma exchange/infusion [PE/PI] or dialysis prior to study entry, the duration of PE/PI treatment, kidney transplant history, mutation, and anti-CFH autoantibody testing). For all 3 populations, the distribution of initial aHUS presentation was assessed by age at presentation and sex.

### Results

#### Patient Demographics and Clinical Characteristics

A total of 37 Canadian patients were enrolled (15 pediatric and 22 adult patients) between February 2014 and May 2017, most of whom were female (62.2%). A family history of HUS was reported in 3 patients (5.4%; Table 1). The median age at initial aHUS presentation was 25.9 (IQR = 6.7-51.7) years; 4.1 (IQR = 1.8-8.8) years in pediatric patients and 50.8 (IQR = 32.3-58.0) years in adults. Male and female patients with aHUS were of similar age at initial presentation (median age for males: 23.9 [IQR = 7.9-57.1] years; median age for females: 25.9 [IQR = 5.5-51.7] years) (Figure 1).

More adults versus children had been dialyzed prior to study entry (63.6% vs 40.0%), with 36.4 and 6.7% of these patients requiring chronic dialysis (lasting for ≥3 months). Of those patients undergoing kidney transplantation, all were adults (Table 1).

#### Medical History and Patient Characteristics

Most of the patients had no conclusive genetic or anti-CFH antibody information available (Table 2). Only 15 patients (8 children and 7 adults) were tested for genetic mutations; 8 patients had their results reported in the Global aHUS Registry,
of whom 2 (2/8; 25%) were reported to have an identified mutation or positive anti-CFH antibodies. Nearly all patients (35/37; 94.6%) were reported as having no precipitating factors for aHUS prior to diagnosis. Of the 2 patients with precipitating factors prior to aHUS diagnosis, neither had conclusive genetic or anti-CFH antibody information available: 1 adult had had a prior kidney transplant nearly 12 years prior to aHUS diagnosis, and 1 child had a prior malignancy just over 2 years prior to aHUS diagnosis.

**Outcomes**

Nine patients (8 adults and 1 child) experienced ESRD, with ESRD-associated risk factors shown in Table 3. After initial presentation, there appears to be a trend that children are less likely to experience ESRD than adults. Five-year ESRD-free survival probability in children was 0.93, versus 0.56 in adults ($P = .05$; Figure 2A), and in females it was 0.77, versus 0.62 in males ($P = .116$; Figure 2B).
Renal and Extrarenal Organ Manifestations

Based on a descriptive analysis, renal manifestations were identified in all patients at initial presentation and over two-thirds of patients (68.4%) during the chronic phase (study entry ≥6 months after initial presentation; Figure 3A). Extrarenal manifestations also occurred in more patients during the initial presenting phase than those in the chronic phase, with differences of >15% between the phases for gastrointestinal (61.1% vs 15.8%) and central nervous system sites (38.9% vs 5.3%). All children and adults experienced renal manifestations (Figure 3B), with subtle differences in extrarenal manifestations. Fewer children than adults experienced gastrointestinal manifestations (50.0% vs 70.0%), but more children than adults experienced pulmonary manifestations (37.5% vs 10.0%).

Discussion

In this analysis of Canadian patients enrolled over 3 years in the Global aHUS Registry, there was a differential sex risk of aHUS: while the male:female ratio at initial presentation was equal in children, among adult patients, two-thirds were female. Pediatric patients were less likely to experience ESRD events than adult patients, and as expected, more patients reported renal manifestations during the initial phase. Differences in extrarenal manifestations were observed depending on disease phase and whether aHUS occurred in childhood or adulthood. Our findings of Canadian clinical practice up to 2017 are consistent with recent data from a larger analysis of 851 patients enrolled up to 2015 in the Global aHUS Registry. A differential sex risk of aHUS pre- and post-puberty was seen for Canadian (male:female ratio of 1:1 in pediatric patients; 1:2 in adult patients) and global patients (1.3:1 in pediatric patients; 1:2 in adult patients). In addition, nearly all Canadian and global patients had no reported precipitating factors prior to aHUS diagnosis, approximately half had no conclusive genetic or anti-CFH antibody information, and of those tested, few had mutations or anti-CFH antibodies detected. In the larger global data set, being a child at initial presentation appeared to decrease the risk for ESRD (adjusted HR = 0.55 [95% CI = 0.41-0.73]). In addition, Schaefer et al observed better 5-year ESRD survival in children versus adults (73% vs 51%; P < .001), but no 5-year ESRD survival benefit was seen for females versus males, similar to our observations. There are apparent differences between the Canadian and

| Variable | Patients, n | ESRD events, n | Unadjusted HR (95% CI) | Adjusted HR (95% CI)a |
|----------|-------------|----------------|------------------------|-----------------------|
| Pediatric versus adult at initial presentation | | | | |
| Adult | 21 | 8 | 1.00 | 1.00 |
| Pediatric | 15 | 1 | 0.17 (0.02-1.33) | 0.13 (<0.01-1.64) |
| Sex | | | | |
| Female | 23 | 5 | 1.00 | 1.00 |
| Male | 13 | 4 | 3.16 (0.70-14.34) | 4.25 (0.60-30.06) |
| Race | | | | |
| White | 31 | 9 | 1.00 | 1.00 |
| Non-white | 5 | 0 | <0.01 (<0.01) | <0.01 (<0.01) |
| Family history of aHUS | | | | |
| No | 34 | 8 | 1.00 | 1.00 |
| Yes | 2 | 1 | 1.11 (0.13-9.46) | 2.72 (0.14-52.42) |
| Time from initial presentation to diagnosis, d | | | | |
| Zero | 8 | 2 | 1.00 | 1.00 |
| 1-14 | 14 | 3 | 1.46 (0.24-9.02) | 1.35 (0.19-9.62) |
| 15-30 | 5 | 2 | 5.48 (0.58-51.70) | 2.66 (0.18-40.35) |
| 31-180 | 5 | 0 | <0.01 (<0.01) | <0.01 (<0.01) |
| >180 | 4 | 2 | 2.19 (0.30-15.81) | 1.00 (0.13-7.92) |
| Any precipitating factorb | | | | |
| No | 35 | 9 | 1.00 | 1.00 |
| Yes | 1 | 0 | <0.01 (<0.01) | <0.01 (<0.01) |

Note. ESRD = end-stage renal disease; HR = hazard ratio; CI = confidence interval; aHUS = atypical hemolytic uremic syndrome.

aHR adjusted for full Cox regression model, including all covariates in the table.

bPrecipitating factors included transplantation, malignancy, pregnancy, autoimmune disease, or malignant hypertension prior to aHUS presentation.

HRs and 95% CIs for genes and covariates among all patients in ESRD. Patients with kidney transplant prior to aHUS presentation and those with treatment initiation at aHUS presentation were excluded from this analysis.
the Global aHUS Registry data in extrarenal manifestations depending on disease phase and the patient’s age, perhaps reflecting differences in underlying precipitating factors (eg, malignancy, bone marrow transplant). In the current analysis of Canadian patients’ data, gastrointestinal manifestations were reported by few children, whereas more children than adults experienced pulmonary manifestations. In the global analysis, gastrointestinal manifestations were
reported by more children versus adults during the initial presenting phase (47% vs 33%), but during the chronic phase, they were reported by more adults versus children (26% vs 18%). During both phases, more adults than children reported pulmonary manifestations (20% vs 12%).14 With our current knowledge, it remains unclear why disease phase and the patient’s age should affect the occurrence of extrarenal manifestations but one possible explanation is the difference in sample size between the current analysis and the Global aHUS Registry analysis (37 vs 851 patients). This highlights the need for large registry databases to help guide and inform clinical decision-making when managing patients with aHUS.

A key challenge faced by Canadian clinicians, as opposed to clinicians in some European countries, is that provincial governments in Canada and supplemental private insurances differ in the payment coverage for diagnostic testing and medications. Indeed, access to genetic and biomarker testing and obtaining results in a timely manner have been a considerable challenge for Canadian clinicians. Recently, the availability of genetic and functional complement testing has substantially improved in Canada, along with the development of a Canadian Expert Consensus for the diagnosis of Canadian patients with aHUS. The publication of these guidelines will provide clinicians with practical and timely advice into how to best diagnose this ultra-rare disease. In addition, a personalized monitoring plan approach is being implemented in some centers using the genetic profile and monitoring of complement activity (using biomarkers such as CH50, C5b-9, C3). It is expected that this center-level, personalized approach will be refined and adopted more widely, or nationally. Pediatric and adult patients present specific management challenges due to a different spectrum of comorbidities, triggering conditions, and renal outcome.

This evaluation provides insight into the diagnosis and management of aHUS in Canadian patients over 3 years and the challenges faced. At the national level, improvements are needed in the diagnosis and further characterization of aHUS (including genetic and anti-CFH antibody testing). We also need a better understanding of triggering factors of aHUS, extrarenal manifestations and risk factors for chronic kidney disease in aHUS. However, raising awareness of aHUS, prompt diagnosis and treatment, and access to optimized treatment have the potential to improve outcomes and reduce the disease burden for affected patients and families.

**Ethics Approval and Consent to Participate**

Written informed consent was provided by patients or their parents or guardians, as deemed applicable by institutional review boards or independent ethics committees.

**Consent for Publication**

All authors consent to the publication of this study.

**Availability of Data and Materials**

The data and materials are not available for this study.

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**Declaration of Conflicting Interests**

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this...
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