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Children and Adults With Thrombotic Thrombocytopenic Purpura Associated With Severe, Acquired Adamts13 Deficiency: Comparison Of Incidence, Demographic and Clinical Features

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Background. Thrombotic thrombocytopenic purpura (TTP) associated with severe, acquired ADAMTS13 deficiency is uncommonly reported in children. The incidence, demographic, and clinical features of these children, compared to adults, have not been described. ***Procedures.*** This study focused on children (<18 years old) and adults with TTP associated with severe, acquired ADAMTS13 deficiency, defined as activity <10%. The incidence rates for TTP in children and adults were calculated from patients enrolled in the Oklahoma TTP–HUS (Hemolytic–Uremic syndrome) Registry, 1996–2012. To describe demographic and clinical features, children with TTP were also identified from a systematic review of published reports and from samples sent to a reference laboratory for analysis of ADAMTS13. ***Results.*** The standardized annual incidence rate of TTP in children was 0.09×10^6 children per year, 3% of the incidence rate among adults (2.88×10^6 adults per year). Among the 79 children who were identified (one from the Oklahoma Registry, 55 from published reports, 23 from the reference laboratory), TTP appeared to be more common among females, similar to the relative increased frequency of women among adults with TTP, and more common in older children. Clinical data were available on 52 children; the frequency of severe renal failure, relapse, treatment with rituximab, and systemic lupus erythematosus in these children was similar to adults with TTP. ***Conclusions.*** TTP associated with severe, acquired ADAMTS13 deficiency is uncommon in children. The demographic and clinical features of these children are similar to the features of adults with TTP. Pediatr Blood Cancer 2013;60:1676–1682.

Key words: children; disparities; incidence; thrombotic thrombocytopenic purpura; TTP

INTRODUCTION

Thrombotic thrombocytopenic purpura (TTP) associated with severe, acquired ADAMTS13 deficiency, caused by autoantibodies that inhibit ADAMTS13 activity [1,2], is uncommonly reported in children. Most published reports describe only a single child. Although, a recent report from a referral laboratory in Japan described 17 children (age ≤15 years), this represented only 6% of all 283 patients with TTP associated with acquired ADAMTS13 deficiency across 11 years, 1998–2008 [3]. In our experience with the Oklahoma TTP–HUS (Hemolytic–Uremic syndrome) registry, only one child (age <18 years old) has been identified among all 74 patients with TTP associated with acquired ADAMTS13 deficiency since routine measurement of ADAMTS13 began in November 1995 through December 2012. The demographic and clinical features of children with TTP associated with severe, acquired ADAMTS13 deficiency have not been described and compared to the demographic and clinical features of adults. Therefore the aims of this study were [1] to estimate the incidence of TTP associated with severe, acquired ADAMTS13 deficiency in children (<18 years old) compared to adults in the Oklahoma Registry region and [2] to identify children with TTP associated with severe, acquired ADAMTS13 deficiency from published reports and laboratory referrals to compare their demographic and clinical features to the adult patients in the Oklahoma Registry.

METHODS

The Oklahoma TTP–HUS Registry

The Oklahoma TTP–HUS Registry is a population-based inception cohort of consecutive patients identified by a request to the Oklahoma Blood Institute (OBI) for plasma exchange treatment for TTP or HUS [2,4,5]. All patients in 58 of Oklahoma's 77 counties, without selection or referral bias, are included in the Registry because [1] the Oklahoma Blood Institute is the sole provider of plasma exchange for all hospitals in these counties and [2] plasma exchange is the standard treatment in this region for all adults diagnosed with TTP or HUS, children who are diagnosed with TTP or atypical HUS, and children diagnosed with typical, diarrhea-associated HUS who have severe neurologic complications. All identified patients have been enrolled. The Registry is approved by the Institutional Review Boards of the University of Oklahoma Health Sciences Center and all participating hospitals.

ADAMTS13 activity was measured by both quantitative immunoblotting and a fluorogenic assay using FRETS-VWF73 substrate in serum collected immediately before the first plasma exchange since November 13, 1995, when systematic serum

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Conflict of interest: The authors have no conflict with this topic or these data. Drs. George and Kremer Hovinga serve as consultants for Baxter, Inc. for the development of rADAMTS13 as a potential treatment for TTP. Dr. George has served as a consultant for Alexion, Inc. for the development of eculizumab as a treatment for aHUS.

Reese and Muthurajah contributed equally to this work.

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collection from all patients enrolled in the Oklahoma Registry was begun [2]. A severe deficiency was defined as ADAMTS13 activity <10% by either method. Inhibitor activity was determined by measuring residual ADAMTS13 activity in normal plasma, using the FRETS method, after incubation with patient serum [2]. Data presented for the adult patients with severe, acquired ADAMTS13 deficiency were updated from our previous publication [2]. The definition of severe, acute renal failure was previously described [4].

Determination of Incidence Rates for Oklahoma Registry Patients

Each patient was classified by age, sex, and race. Patients' race was defined by the investigators and was categorized as black or non-black. Census data for race were defined as black alone or non-black for all other racial designations. Overall, age-, sex-, and race-specific incidence rates were calculated using 2000 and 2010 census population data for each of the 58 counties of the Registry region. Population data from the 2000 census were used to calculate the person-time for patients who were diagnosed in 1996–2004 and population data from the 2010 census were used to calculate the person-time for the patients who were diagnosed in 2005–2012.

To make the Oklahoma Registry data generalizable to the US population, our incidence rates were standardized for age, sex, and race using the age, sex, and race distribution of the US population. US population data for standardization were obtained from the 2000 census data; 2000 census data for age, sex, and race were similar to 2010 census data. For the overall, stratum-specific, and standardized incidence rates, 95% confidence intervals were calculated based on the Poisson distribution when the total number of observed TTP patients was less than 100. When the total number of observed TTP patients was 100 or more, the normal distribution was used.

Identification of Children With TTP Associated With Severe, Acquired ADAMTS13 Deficiency

Systematic literature review. Published reports of children with TTP associated with severe, acquired ADAMTS13 deficiency were identified by searching five databases. Ovid interface was used to search the MEDLINE and EMBASE (Excerpta Medica Database) databases and the Cochrane Database of Systematic Reviews. MEDLINE and additional sources were searched using the PubMed interface. The EBSCO interface was used to search CINAHL (Cumulative Index to Nursing and Allied Health) database. The search strategy identified articles that included [1] a TTP or HUS-related key-word or Medical Subject Heading (MeSH) [*thrombotic thrombocytopenic purpura, TTP, hemolytic-uremic syndrome, HUS, thrombotic thrombocytopenic purpura-hemolytic uremic syndrome, TTP–HUS, thrombotic microangiopathy, thrombotic microangiopathies*] [2] a key-word or MeSH term to identify children [*infant, child, children, preschool, middle school, high school, pediatric, pediatrics*], and [3] the term *ADAMTS13* in the title or available text. If an article's title suggested that individual patient data for children with TTP were described, the abstract was selected for review. If the abstract confirmed that the article described children with TTP, the complete article was reviewed. Bibliographies of the articles selected for review and the files of the authors were also searched to identify additional articles. Age <18 years was selected to define children since this is a common criterion for pediatric practice and children's hospitals. Severe ADAMTS13 deficiency (activity <10%) was required and evidence for acquired ADAMTS13 deficiency was either the presence of a demonstrable ADAMTS13 inhibitor and/or recovery of ADAMTS13 activity to normal during clinical remission. For children with severe acquired ADAMTS13 deficiency, age, race, gender and clinical features were recorded.

Reference laboratory experience. Children <18 years old with ADAMTS13 activity <10% and a documented ADAMTS13 inhibitor were also identified from samples referred for ADAMTS13 activity measurement to the Central Hematology Laboratory of the Inselspital, University of Bern, Switzerland, 2002–2011. Most samples were from Europe and most of the European samples were from Germany and Switzerland. Age and gender were available for all patients but clinical data were not available. Therefore these data were only used for the assessment of patients' age and gender.

TABLE I. Annual Incidence of TTP per 10^6 Person-Years Over a 17 Year Period

Patient groups	N	Incidence rates (95% CI)	Standardized incidence rates (95% CI)	Incidence rate ratios (95% CI)
All patients	333	8.14 (7.26, 9.01)	8.92 (8.57, 9.27)	—
All patients with ADAMTS13 activity measurement	312	7.62 (6.78, 8.46)	8.35 (8.02, 8.69)	—
Adults	289	9.42 (8.33, 10.50)	13.19 (12.70, 13.69)	4.27 (3.83, 5.25)
Children	23	2.24 (1.33, 3.16)	3.09 (2.69, 3.50)	
Patients with ADAMTS13 <10%	73	1.78 (1.40, 2.24)	2.17 (2.00, 2.34)	—
Adults	72	2.35 (1.84, 3.00)	2.88 (2.66, 3.12)	31.62 (14.68, 68.10)
Children	1	0.098 (0.003, 0.543)	0.091 (0.039, 0.20)	
Black	26	8.68 (5.67, 12.71)	8.78 (7.79, 9.77)	7.09 (6.05, 8.31)
Non-black	47	1.23 (0.91, 1.65)	1.24 (1.10, 1.38)	
Women	56	2.71 (2.05, 5.52)	3.27 (2.97, 3.57)	3.19 (2.65, 3.85)
Men	17	0.84 (0.49, 1.34)	1.02 (0.86, 1.19)	

Data for adults are updated from 2005 [29]. These data include 73 adult patients (vs. 23 in our previous study) identified over 17 years (vs. 8.5 years in our previous study) using the current definition of severe ADAMTS13 deficiency (<10%, vs. <5% in our previous study). Our previous study included the one child together with 22 adults.

Statistical Analysis

Descriptive statistics were used for the presentation of children's data since the criteria for selection of children for publication and for referral for reference laboratory testing are unknown.

RESULTS

Oklahoma Registry Patients

Incidence rate estimates were determined for patients enrolled in the Oklahoma Registry who had their initial episode between January 1, 1996 and December 31, 2012, to include only complete years. This time period excluded 108 patients enrolled January 1, 1989–December 31, 1995; one patient with ADAMTS13 activity <10% who had her initial episode in 1995 was excluded.

During the 17 years, January 1, 1996–December 31, 2012, all 356 consecutive patients for whom plasma exchange was requested for treatment of TTP or HUS were enrolled in the Registry. Seven patients were excluded from this analysis because they lived outside the 58-county Registry region. Six patients were excluded because they had been treated for a previous episode of TTP, either before 1996 or outside of the Registry region. Nine patients were excluded because they were diagnosed by kidney biopsy, not by clinical criteria. One patient was excluded because she has hereditary ADAMTS13 deficiency. Therefore incidence calculations were based on 333 patients who lived within the Registry region and who were clinically diagnosed with their initial episode of acquired TTP or HUS and plasma exchange treatment was requested. Among these 333 patients, 312 (94%) had ADAMTS13 activity measured immediately before beginning their first plasma exchange treatment. Among the 312 patients in whom ADAMTS13 activity was measured, 289 (93%) were adults and 23 (7%) were children. Seventy-three (25%) of the 289 adults had ADAMTS13 activity <10%. Only one (4%) of the 23 children had ADAMTS13 activity <10%, a 9 year-old white male who has had no evidence of other autoimmune disorders, has had two relapses, was treated with rituximab, and recovered.

Incidence and Demographic Features of Oklahoma Registry Patients

Table I presents incidence rates [1] for all 333 patients treated for their first episode of clinically diagnosed TTP or HUS in the registry region, 1996–2012 [2], for the 312 patients who had ADAMTS13 activity measured, included separate analyses for adults and children, and [3] for the 73 patients with ADAMTS13 activity <10%. Among patients with ADAMTS13 activity <10%, incidence rates are presented for children (<18 years old) and adults (≥18 years old). For patients with ADAMTS13 activity <10%, the standardized incidence rate is more than 30-fold higher in adults compared to children, more than sevenfold higher in blacks compared to non-blacks, and more than threefold higher in women compared to men. Among the 47 non-black patients with ADAMTS13 activity <10%, 45 were white and two were Native American. The age and gender distribution of all 73 patients with ADAMTS13 activity <10% are presented in Figure 1.

Demographic Features of Children With TTP Associated With Severe, Acquired ADAMTS13 Deficiency

In addition to the one child from the Oklahoma Registry, the systematic literature review identified 55 children <18 years old with TTP associated with severe, acquired ADAMTS13 deficiency in 24 articles (Table II) [3,6–28]. Twenty-three additional children <18 years old with ADAMTS13 activity <10% and a demonstrable ADAMTS13 inhibitor were identified from the records of the Central Hematology Laboratory of the Inselspital, University of Bern, Switzerland, 2002–2011. The age and gender of these 79 children are illustrated in Figure 2 and Table III. There appeared to be more females than males and older children (ages 9–17 years) than younger children (ages 0–8 years). Children's race was not assessed because it was documented in only 15 of the 55 children in published case reports.

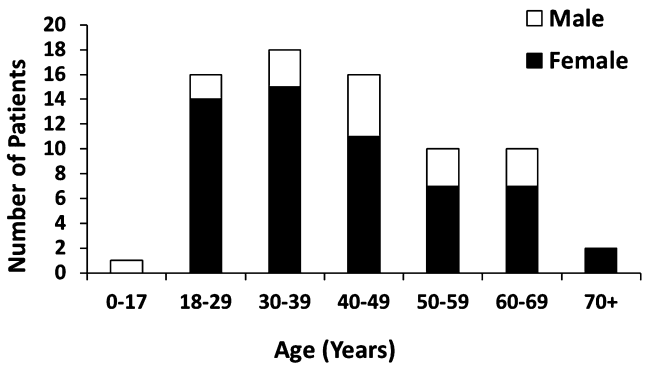

Fig. 1. Age and gender distribution of 73 patients (1 child <18 years old, 72 adults) with TTP associated with sever, acquired ADAMTS13 deficiency (activity <10%) in the Oklahoma TTP–HUS Registry, 1996–2012.

Clinical Features of Children With TTP Associated With Severe, Acquired ADAMTS13 Deficiency

In addition to the Oklahoma Registry patient, data for most of the clinical features that we assessed were available for 51 of the 55 children in 23 of the 24 published case reports; no clinical data were described in one report [12] and no clinical data were available for the children identified by the reference laboratory. Selected clinical features of these 52 children and of the 72 adults in the Oklahoma Registry are presented in Table IV. Death was reported for only one child (Patient #42, Table II) [3]. Although death from the initial episode of TTP appeared to be less in children, other clinical features were similar. Severe renal failure was uncommon among the reported children. Among the four children with severe renal failure, two had typical clinical features of diarrhea-associated HUS, including evidence for infection with *E. coli* O157:H7 [6,10], one had a previous kidney transplant for Denys–Drash syndrome [14], and one child was described as having a serum creatinine of 3.8 mg/dl requiring dialysis [11]. Severe renal failure was also uncommon among adults with TTP associated with severe, acquired ADAMTS13 deficiency. Among the seven adults with severe renal failure, four patients were critically ill and died during their initial episode of TTP. Among the 10 children who were reported to have an additional diagnosis of systemic lupus erythematosus (SLE), three had a previous diagnosis, three were diagnosed with SLE at the time of their initial episode of TTP, and four were diagnosed during follow-up (6–54 months, median 38 months). Among the eight adults with an additional diagnosis of systemic lupus erythematosus (SLE), four had a previous diagnosis,

TABLE II. Children Less Than 18 Years Old With TTP and Severe Acquired ADAMTS13 Deficiency

No.	Source	Year	Age	Sex	Renal	SLE	Rituximab	Relapse
1	Oklahoma registry	2000	9	M	0	0	+	+
2	Hunt [6]	2001	1	M	+	…	…	…
3	Gungor [7]	2001	12	F	0	+	…	…
4	Ashida[a] [8]	2002	0.75	F	0	…	…	…
5	Robson [9]	2002	8	M	0	…	…	…
6	Veyradier [10]	2003	4	F	+	…	…	…
7	Horton [11]	2003	1	F	0	…	…	…
8	Horton [11]	2003	8	F	0	…	…	+
9	Horton [11]	2003	11	F	+	…	…	…
10	Horton [11]	2003	16	M	0	…	…	+
11	Schneppenheim [12]	2003	0.92	M	…	…	…	…
12	Schneppenheim [12]	2003	6	M	…	…	…	…
13	Schneppenheim [12]	2003	9	F	…	…	…	…
14	Schneppenheim [12]	2003	11	F	…	…	…	…
15	Matsumoto [13]	2004	14	F	…	…	…	…
16	Ulinski [14]	2006	9	M	+	…	…	…
17	Curtillet [15]	2006	14	M	…	…	+	…
18	Moskowitz [16]	2009	5	F	0	…	…	…
19	Albaramki [17]	2009	6	M	0	…	+	+
20	Albaramki [17]	2009	15	F	0	…	+	+
21	Binder [18]	2009	16	F	0	+	+	…
22	McDonald [19]	2010	4	F	0	…	+	…
23	McDonald [19]	2010	9	F	0	+	…	+
24	McDonald [19]	2010	12	F	0	…	+	+
25	McDonald [19]	2010	13	F	0	…	+	+
26	McDonald [19]	2010	13	F	0	…	+	…
27	McDonald [19]	2010	14	F	0	…	+	…
28	McDonald [19]	2010	17	F	0	…	+	…
29	Sato[a] [20]	2010	0.75	M	0	…	…	+
30	Harambat [21]	2011	10	M	0	…	+	…
31	Thampi [22]	2011	9	F	0	+	…	…
32	Muscal [23]	2011	2	M	0	+	…	+
33	Muscal [23]	2011	11	F	0	+	…	+
34	Muscal [23]	2011	11	F	0	…	…	+
35	Muscal [23]	2011	13	F	0	+	…	…
36	Muscal [23]	2011	17	F	0	+	…	+
37	Jayabose [24]	2011	10	F	…	…	+	+
38	Pelras [25]	2011	2	F	0	…	…	…
39	Morishima [26]	2012	11	F	0	…	…	…
40	Yagi [3]	2012	1	M	0	…	…	…
41	Yagi [3]	2012	1	M	0	…	…	…
42	Yagi [3]	2012	1	F	0	…	…	+
43	Yagi [3]	2012	7	M	0	…	+	…
44	Yagi [3]	2012	8	F	0	+	…	…
45	Yagi [3]	2012	10	M	0	…	…	…
46	Yagi [3]	2012	11	M	0	…	…	…
47	Yagi [3]	2012	11	F	0	…	…	…
48	Yagi [3]	2012	11	F	0	…	…	…
49	Yagi [3]	2012	12	F	0	+	…	…
50	Yagi [3]	2012	13	F	0	…	…	…
51	Yagi [3]	2012	14	F	0	…	…	…
52	Yagi [3]	2012	14	M	0	…	…	…
53	Yagi [3]	2012	15	M	0	…	…	+
54	Yagi [3]	2012	15	M	0	…	…	…
55	Narayana [27]	2012	9	F	0	…	+	+
56	Kawasaki [28]	2013	0.17	M	0	…	…	…
57	Bern laboratory	2002–11	0.7	F	…	…	…	…
58	Bern laboratory	2002–11	1	M	…	…	…	…

(*Continued*)

TABLE II. (*Continued*)

No.	Source	Year	Age	Sex	Renal	SLE	Rituximab	Relapse
59	Bern laboratory	2002–11	1	F	…	…	…	…
60	Bern laboratory	2002–11	1	M	…	…	…	…
61	Bern laboratory	2002–11	3	F	…	…	…	…
62	Bern laboratory	2002–11	4	M	…	…	…	…
63	Bern laboratory	2002–11	4	M	…	…	…	…
64	Bern Laboratory	2002–11	5	F	…	…	…	…
65	Bern laboratory	2002–11	5	M	…	…	…	…
66	Bern laboratory	2002–11	8	M	…	…	…	…
67	Bern laboratory	2002–11	10	F	…	…	…	…
68	Bern laboratory	2002–11	10	F	…	…	…	…
69	Bern laboratory	2002–11	10	M	…	…	…	…
70	Bern laboratory	2002–11	12	M	…	…	…	…
71	Bern laboratory	2002–11	12	M	…	…	…	…
72	Bern laboratory	2002–11	13	F	…	…	…	…
73	Bern laboratory	2002–11	15	F	…	…	…	…
74	Bern laboratory	2002–11	15	F	…	…	…	…
75	Bern laboratory	2002–11	16	F	…	…	…	…
76	Bern laboratory	2002–11	17	F	…	…	…	…
77	Bern laboratory	2002–11	17	F	…	…	…	…
78	Bern laboratory	2002–11	17	F	…	…	…	…
79	Bern laboratory	2002–11	17	F	…	…	…	…

[a]The two children reported by Ashida [8] and Sato [20] were also reported by Yagi [3] and were excluded from the Yagi data in this Table. Only one reported child was described as dying from her episode of TTP (Patient #42). For renal function, 0 indicates a report either as normal or that the serum creatinine was only mildly and transiently elevated; + indicates a report of severe renal failure, requiring dialysis in three patients (#2, 9, 16). When renal function, the diagnosis of SLE, treatment with rituximab, or occurrence of relapse was not explicitly described, the results are indicated as not reported (…). No clinical data were available for patients who were identified by samples sent to the Bern reference laboratory.

two were diagnosed with SLE at the time of the initial episode of TTP, and two were diagnosed during follow-up (5 and 68 months).

DISCUSSION

Data from the Oklahoma TTP–HUS Registry confirmed that TTP associated with severe, acquired ADAMTS13 deficiency is rare in children <18 years old. The standardized annual incidence rate is 0.09×10^6 children per year, 3% of the incidence rate among adults. Our current data for the standardized annual incidence rate of all patients with TTP associated with severe, acquired ADAMTS13 deficiency, 2.17×10^6 people per year was based on 73 patients with ADAMTS13 activity <10% identified over 17 years, 1996–2012. These data were consistent with our previous report on 24 patients with ADAMTS13 <5% identified over 8.5 years, 1996–2004 [29].

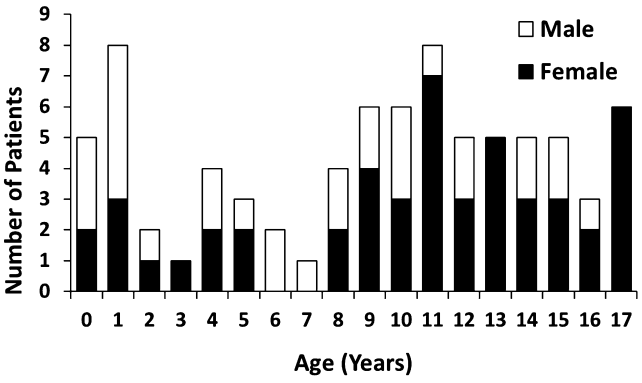

Fig. 2. Age and gender distribution of 79 children (age <18 years old), including 1 child from the Oklahoma Registry, 55 children published in 24 reports, and 23 patients from a reference laboratory, Bern, Switzerland.

Children, especially children less than five years old who present with thrombocytopenia and microangiopathic hemolytic anemia with abdominal pain and diarrhea, meet diagnostic criteria for typical HUS. Typical HUS is now described as STEC–HUS because the etiology is infection by Shiga toxin-producing *E. coli* (STEC), principally *E. coli* O157:H7 [30]. The annual incidence of STEC-HUS is 61×10^6 children less than 5 years old [31], much greater than the incidence of TTP. Children with STEC–HUS commonly have severe renal failure. Ten percent of children diagnosed with HUS, because they have thrombocytopenia, microangiopathic, hemolytic anemia, and renal failure, do not have a prodrome of abdominal pain and diarrhea and are therefore described as atypical HUS, or aHUS [31]. Children with aHUS may have a genetic abnormality allowing uncontrolled activation of the complement system [31]. When a child presents with thrombocytopenia and microangiopathic hemolytic anemia but without a prodrome of abdominal pain and diarrhea, it is appropriate to measure ADAMTS13 activity. ADAMTS13 activity is typically normal in children with both STEC–HUS and aHUS; a severe deficiency of ADAMTS13 defines children with TTP [6,10,31]. Renal failure is uncommon in children with TTP, but it may occur. The limitations of this algorithm are emphasized by the published reports of two children with both STEC-HUS and TTP associated with severe ADAMTS13 deficiency [6,10]. This occurrence of concurrent syndromes may be the result of Shiga toxin triggering the onset of an acute episode of TTP in a child with severe ADAMTS13 deficiency, similar to the mechanism of Shiga toxin causing acute

TABLE III. Age and Gender of 79 Children With TTP Associated With Severe Acquired ADAMTS13 Deficiency

Age	Boys	Girls	Total
0–8	17	13	30
9–17	13	36	49
Total	30	49	79

Data are for the one child from the Oklahoma Registry, 55 children from published reports, and 23 children from the reference laboratory.

TABLE IV. Clinical Features of Children and Adults With TTP Associated With Severe Acquired ADAMTS13 Deficiency

Clinical feature	Children (N = 52)	Adults (N = 72)
Severe renal failure	4 of 49 (8%)	7 (10%)
Additional diagnosis of systemic lupus erythematosus	10 (19%)	8 (11%)
Treatment with rituximab	15 (29%)	16 (22%)
Death (from initial episode)	1 (2%)	13 (18%)
Relapse	17 of 51 (33%)	21 of 59 (36%)

Data describing children are for the one child from the Oklahoma Registry and 51 of the 55 children from published reports; one publication [12] reported no clinical data. Three additional published reports did not describe renal function [13,15,24]. Severe renal failure was defined by the use of dialysis in three patients [6,11,14] and by a "course typical of D+ HUS" in one patient [10]. When the diagnosis of SLE, treatment with rituximab, death or relapse were not mentioned, it was assumed that it had not occurred. There were no clinical data for the 23 children from the reference laboratory. Data describing adults with severe renal failure, death and relapse are updated from 2010 [2].

thrombocytopenia and microangiopathic hemolytic anemia in transgenic mice with absent ADAMTS13 [32].

For a child who presents with typical clinical features of STEC–HUS [30], supportive care is appropriate. For a child who presents with thrombocytopenia and microangiopathic hemolytic anemia without a prodrome of abdominal pain and diarrhea, treatment with plasma exchange must be considered. Plasma exchange treatment is essential for patients with TTP [5,33] and is also appropriate for patients with aHUS [31,34].

In children with TTP, the presence of an inhibitor of ADAMTS13 activity or the recovery of ADAMTS13 activity following the acute episode documents an acquired, autoimmune etiology. The prompt and complete response to plasma treatment, the absence of an inhibitor of ADAMTS13 activity, and the persistence of severe ADAMTS13 deficiency following recovery suggest TTP caused by congenital ADAMTS13 deficiency. Congenital ADAMTS13 deficiency can be confirmed by genetic analysis, which is available from the Hereditary TTP Registry (www.ttpregistry.net) [35].

Among adults with severe, acquired ADAMTS13 deficiency there are significant disparities of gender and race, with increased relative incidence rates of women compared to men and of blacks compared to non-blacks. Although the race distribution could not be assessed among children because it was described in only few of the published reports, the gender distribution, with more females than males, was similar to adults. Although TTP associated with severe, acquired ADAMTS13 deficiency in children has been described in infants as young as 2–11 months of age [8,12,20,28], among all identified children, TTP appeared to be more frequent among older children.

In addition to the one child in the Oklahoma Registry, 51 of the 55 published reports of children presented clinical information. Ten (19%) of these 52 children had an additional diagnosis of SLE; 17 (33%) had relapsed; 15 (29%) were treated with rituximab for an initial or relapsed episode. These clinical features are similar to the clinical features of adults with TTP associated with severe, acquired ADAMTS13 deficiency. Among adults, the occurrence of SLE is consistent with the age, race, and gender disparities, with a relative increased frequency of young, black women. These are the same demographic disparities that characterize SLE [36].

The clinical features of autoimmune disorders in children may be distinct from or similar to the disorders in adults. For example, primary immune thrombocytopenia (ITP) in children is distinct from ITP in adults. ITP in children is more common among males, in contrast to the increased relative frequency of women among younger adults, and it is typically an acute and spontaneously remitting disorder, in contrast to the chronic course in adults [37,38]. In contrast, SLE in children is demographically and clinically similar to SLE in adults [39,40]. Data in this report suggest that, similar to SLE, TTP associated with severe, acquired ADAMTS13 deficiency is the same disorder in children and adults.

Interpretation of the data for demographic and clinical features of children is limited by the presumed selection biases for publication of a case report and for sending a sample to a referral laboratory. Data from published reports may be biased to describe exceptional patients, such as infants, children with severe and relapsing TTP for which rituximab was given, and children with an additional diagnosis of SLE. Data from samples sent to the reference laboratory may be affected by similar selection biases. However, these two sources represent a large number of children with TTP who had documented acquired severe ADAMTS13 deficiency. Data from published reports and from the reference laboratory were combined for an estimate of the demographic features. Data from published reports which described clinical features were compared to data describing the clinical features of adults in the Oklahoma Registry. Interpretation of these comparisons is limited by the different methods of identification of children and adults. The data for children may be biased by selection for publication of a case report while the data for adults were identified prospectively, without selection or referral bias. These limitations may be inevitable when the features of a rare disorder are assessed.

Although TTP associated with severe, acquired ADAMTS13 deficiency in children is rare, it appears to be the same disorder that occurs in adults and to require similar management. Children who recover from their initial episode of TTP associated with severe, acquired ADAMTS13 deficiency require the same long-term follow-up that is required for adults, to be alert for relapsed episodes and for other autoimmune disorders, such as SLE.

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