Different disparities of gender and race among the thrombotic thrombocytopenic purpura and hemolytic-uremic syndromes

Deirdra R. Terrell,[1]* Sara K. Vesely,[1] Johanna A. Kremer Hovinga,[3] Bernhard Lämmle,[3] and James N. George[1,2]

Thrombotic thrombocytopenic purpura (TTP) and hemolytic-uremic syndrome (HUS) represent multiple disorders with diverse etiologies. We compared the gender and race of 335 patients enrolled in the Oklahoma TTP-HUS Registry across 21 years for their first episode of TTP or HUS to appropriate control groups. The relative frequency of women and white race among patients with TTP-HUS-associated with a bloody diarrhea prodrome and the relative frequency of women with quinine-associated TTP-HUS were significantly greater than their control populations. The relative frequency of women and black race among patients with idiopathic TTP and TTP-associated with severe ADAMTS13 deficiency was significantly greater than their control populations. The relative frequency of black race among patients who had systemic lupus erythematosus (SLE) preceding TTP was significantly greater than among a population of patients with SLE, and the relative frequency of black race among patients with other autoimmune disorders preceding TTP was significantly greater than their control population. No significant gender or race disparities were present among patients with hematopoietic stem cell transplantation-associated thrombotic microangiopathy, TTP associated with pregnancy, or TTP associated with drugs other than quinine. The validity of these observations is supported by the enrollment of all consecutive patients across 21 years from a defined geographic region, without selection or referral bias. These observations of different gender and race disparities among the TTP-HUS syndromes suggest the presence of different risk factors and may serve as starting points for novel investigations of pathogenesis. Am. J. Hematol. 85:844–847, 2010.

Introduction

Although syndromes described as thrombotic thrombocytopenic purpura (TTP) and hemolytic-uremic syndrome (HUS) are all characterized clinically by thrombocytopenia and microangiopathic hemolytic anemia [1] and pathologically by thrombotic microangiopathy (TMA) [2], they represent multiple disorders with diverse pathogenetic factors. Pathogenesis may include genetic abnormalities causing deficiency of ADAMTS13 [3] or complement regulatory components [4], immunologic disorders, such as autoantibodies to ADAMTS13 [5] and complement regulatory factor H [6], and drug-dependent antibodies involving quinine [7,8], toxic disorders such as hemolytic uremic syndrome caused by Shiga toxin-producing *E. coli* infection [9], and the adverse effects of allogeneic hematopoietic stem cell transplantation (HSCT) [10]. We have previously reported the increased relative frequency of women and blacks among patients with acquired severe ADAMTS13 deficiency [11,12]. Subsequently, distinct disparities of gender and race among other categories of these syndromes have become apparent. To document the occurrence of disparities among the TTP and HUS syndromes, we compared the gender and race of patients in the Oklahoma TTP-HUS Registry to control populations of the Registry region or to other appropriate control groups.

Methods

The Oklahoma TTP-HUS registry. The Registry, established in January 1, 1989, is a population-based inception cohort of consecutive patients with a diagnosis of TTP or HUS identified by a request for the Oklahoma Blood Institute (OBI) to provide plasma exchange treatment [11,13]. The OBI is the sole provider of plasma exchange for all hospitals in 58 of Oklahoma's 77 counties. Because patients are primarily adults they are described as TTP; patients with a quinine etiology or bloody diarrhea prodrome are described as TTP-HUS to emphasize their predominant renal involvement. Patients' racial distribution was described as white, black, and other; other was predominantly Native American and Asian. The Registry is approved by the institutional review boards of the University of Oklahoma Health Sciences Center and each participating hospital.

Assignment of patients to clinical categories. Categories related to associated conditions and potential etiologies were: (1) following allogeneic HSCT, (2) pregnant/postpartum, (3) drug-association, (4) bloody diarrhea prodrome, (5) additional/alternative disorder, and (6) idiopathic [11,13]. The drug-association category was separated into two subgroups: (1) quinine-associated and (2) all other drug-associated cases. The category of additional/alternative disorders was separated into three subgroups: (1) patients with a previous diagnosis of systemic lupus erythematosus (SLE), (2) patients with a previous diagnosis of other autoimmune disorders, and (3) patients with other additional/alternative disorders.

Comparison groups. Patients in the categories designated as quinine-associated, other drug-associated, bloody diarrhea prodrome, previous diagnosis of autoimmune disorders other than SLE, idiopathic, and patients with ADAMTS13 activity $<10\%$ were compared to the 2000 US Census data for the populations of the 58 counties of the Registry region (http://factfinder.census.gov/home/saff/main.html?_lang = en) [12], since 2000 is the midpoint of the Oklahoma TTP-HUS

[1]Department of Biostatistics and Epidemiology, College of Public Health, The University of Oklahoma Health Sciences Center, Oklahoma City, Oklahoma; [2]Department of Medicine, College of Medicine, The University of Oklahoma Health Sciences Center, Oklahoma City, Oklahoma; [3]Department of Hematology and Central Hematology Laboratory, Inselspital, Berne University Hospital and University of Berne, Switzerland

Conflict of interest: Drs. Terrell, Kremer Hovinga, Lämmle, and George are consultants for Baxter, Inc for rADAMTS13 development; they have no conflicts of interest with the topic or data of this manuscript. Dr. Vesely has no conflicts of interest.

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*Correspondence to: Deirdra R. Terrell, Department of Biostatistics and Epidemiology, CHB 358, The University of Oklahoma Health Sciences Center, P.O. Box 73190, Oklahoma City, OK 73126-0901. E-mail: deirdra-terrell@ouhsc.edu

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TABLE I. Distribution of Gender and Race Among 335 Consecutive Patients With an Initial Episode of Clinically Diagnosed TTP-HUS, 1989–2009

	Gender			Race			
	M	F	*P*	White	Black	Other	*P*
Clinical categories (number of patients)							
HSCT (22)	9 (41%)	13 (59%)	0.078	18 (82%)	4 (18%)	0 (0%)	0.052
HSCT control patients (350)	60%	40%		79%	8%	13%	
Pregnant/postpartum (27)				22 (82%)	2 (7%)	3 (11%)	1.000
Pregnant/postpartum control				78%	10%	12%	
Drug-associated (52)							
Quinine (25)	1(4%)	24 (96%)	<0.001	24 (96%)	0 (0%)	1 (4%)	0.150
Population control	46%	54%		86%	5%	9%	
Other drugs (27)[a]	10 (43%)	17 (57%)	0.254	25 (93%)	2 (7%)	0 (0%)	0.185
Population control	48%	52%		83%	6%	11%	
Bloody diarrhea prodrome (31)	7(23%)	24 (77%)	0.006	30 (97%)	1 (3%)	0 (0%)	0.032
Population control	48%	52%		82%	7%	11%	
Additional/alternative disorders (49)							
Systemic lupus erythematosus (29)	1 (3%)	28 (97%)	0.701	14 (48%)	12 (41%)	3 (11%)	0.003
SLE control (191)	8%	92%		74%	25%	1%	
Other autoimmune disorders (20)[b]	11 (55%)	9 (45%)	0.419	13 (65%)	5 (25%)	2 (9%)	0.009
Population control	46%	54%		84%	6%	10%	
Idiopathic (154)	41 (27%)	113 (73%)	<0.001	104 (68%)	40 (26%)	10 (6%)	<0.001
Population control	48%	52%		81%	7%	12%	
Laboratory category (number of patients)							
ADAMTS13 <10% (65)[c]	12 (18%)	53 (82%)	<0.001	39 (60%)	23(35%)	3 (5%)	<0.001
Population control	50%	50%		79%	8%	13%	
Idiopathic ADAMTS13 <10% (51)	10 (20%)	41 (80%)	0.096	30 (59%)	19 (37%)	2 (4%)	0.220
Idiopathic ADAMTS13 ≥10% (56)	19 (34%)	37 (66%)		42 (75%)	12 (21%)	2 (4%)	

Patients were compared to appropriate comparison groups as described in Methods. Since gender and race distributions in the population change with age, the "Population control" groups were adjusted to match the age distribution of each of the six patient groups which they were compared to. Idiopathic patients with ADAMTS13 activity <10% and ≥10% were compared to each other.

[a] Other drugs were: Mitomycin C (11), Gemcitabine (3), Cyclosporine (3), Ticlopidine (2), BCNU (1), Clopidogrel (1), Cocaine (1), Fosamax (1), Pentostatin (1), Taxotere-Gemcitabine (1), Trimethoprim-Sulfamethoxazole (1), Vancomycin (1).

[b] Other autoimmune disorders were: immune thrombocytopenic purpura/autoimmune hemolytic anemia (5), scleroderma (3), antiphospholipid syndrome (2), rheumatoid arthritis (2), Wegener's granulomatosis (2), bronchiolitis obliterans organizing pneumonia (1), Hamman-Rich syndrome (1), polyarteritis nodosa (1), rapidly progressive glomerulonephritis (1), Sjögren's syndrome (1), vasculitis (1).

[c] Clinical categories for patients with severe ADAMTS13 deficiency were: HSCT (1), pregnancy (3), bloody diarrhea (2), SLE (2), other autoimmune disorder (1), and idiopathic (51). In addition 5 patients were diagnosed with alternative disorders after plasma exchange treatment for TTP had begun.

Registry and it provides gender- and race-specific data by age for each county. For the 58 county Registry regions, men were 49% and women were 51%; white was 80%, black was 8% and other race was 12%. However, gender and race distributions in the population change with age. The percent of women in the Registry region ranged from 48.1 to 51.8% for people less than 65-years old; the percent of women increased to 54.4% for ages 65–74 and to 63.5% for ages over 75 years. The distribution of white, black, and other races in the Registry region population also changed across age groups; the black population decreased steadily from 10.2% for ages less than 15 years to 4.1% for ages over 75 years; the percent of the population that reports that they are white is lowest in the 15- to 24-year-old age group (72.0%) and increases to 90.5% in the over 75-year-old age group. For comparison to the patient categories, the percent gender and race was adjusted to reflect the age distribution of each patient category. The age distribution of each patient category was used in conjunction with the Registry region population data to create expected percents for gender and race for each patient category. For example the age of patients in the quinine-induced TTP-HUS category is older than the Registry region population; therefore the expected percent women is 54% and the expected percent white is 86% which are both higher than for the overall Registry region. Thus we created a control population specific for each patient category.

Patients in the HSCT-TMA category were diagnosed between September 5, 1992 and March 30, 2003. Because the disorders for which they received transplantation may have had gender disparities [14] and because referral of these patients for transplantation may be associated with race disparities [15], these patients were compared to the other 350 patients who had HSCT during the same years (January 1, 1992 to December 31, 2003) but who were not diagnosed with TMA. All 372 HSCT patients had allogeneic, myeloablative procedures.

Patients who were diagnosed with TTP during pregnancy or postpartum were compared to birth certificate data for women who had given birth in Oklahoma in 2000 [16], the mid-point of the Registry.

Patients who were diagnosed with TTP following a previous diagnosis of SLE were compared to a population-based cohort of incident cases of SLE in Allegheny County, PA [17]. The racial distribution of the Allegheny County population (88% white, 11% black, 1% other) [17] was similar to the Registry region population [12].

ADAMTS13 activity measurements. Systematic collection of serum samples immediately before the initial plasma exchange procedure began on November 13, 1995; since that time ADAMTS13 activity has been measured by both quantitative immunoblotting and the FRETS-VWF73 assay [13] on 280 (93%) of 300 patients. Patients with ADAMTS13 activity <10% by either method were designated as having severe ADAMTS13 deficiency [13].

Statistical analysis. Statistical analyses were performed using SAS, version 9.1.3 (SAS Institute, Cary, NC). HSCT and SLE TTP-HUS patients were compared to their appropriate control groups using a chi-square or Fisher's exact test. Other patients were compared to their appropriate control groups by an exact one-way chi-square test. Idiopathic TTP patients with and without ADAMTS13 deficiency were compared to each other by chi-square (gender) or Fisher's exact tests (race).

Results

The Registry enrolled 421 consecutive patients from January 1, 1989 to December 31, 2009. For this analysis, 86 of the 421 patients were excluded. To restrict our analysis to an inception cohort of patients who were enrolled for their first episode of TTP, 11 patients who were enrolled in the Registry at the time of a relapse were excluded. To restrict our analysis to patients who fulfilled clinical diagnostic criteria for TTP, 12 patients who were diagnosed by renal biopsy rather than by clinical criteria were excluded. For accurate comparison to the Registry region population, we analyzed only patients who lived in the 58 Oklahoma counties served by the OBI; therefore four patients who lived outside the 58 county Registry region were excluded. In addition, one patient whose HSCT was not performed at the University of Oklahoma Medical Center (the only allogeneic transplant facility in the Registry region) was excluded

TABLE II. Distribution of Age Among 335 Consecutive Patients With an Initial Episode of Clinically Diagnosed TTP-HUS, 1989–2009

	Age (years)	
	Median (range)	Interquartile range
Clinical categories (number of patients)		
HSCT (22)	32 (12–53)	24–43
Pregnant/postpartum (27)	25 (17–43)	20–30
Drug-associated		
Quinine (25)	60 (35–81)	55–67
Other drugs (27)	53 (17–91)	42–68
Bloody diarrhea prodrome (31)	53 (1–82)	24–68
Additional/alternative disorders		
Systemic lupus erythematosus (29)	38 (14–64)	26–45
Other autoimmune disorders (20)	60 (2–81)	36–72
Idiopathic (154)	49 (2–85)	35–63
Laboratory category		
ADAMTS13 <10% (65)	40 (9–71)	33–50

Patient categories are defined in methods.

because she could not be appropriately compared to the patients who had allogeneic hematopoietic stem cell transplants at the University of Oklahoma Medical Center and who were not diagnosed with TTP. Finally, because this analysis focused on patients whose final diagnosis was TTP, the 58 patients who were diagnosed with an alternative/additional disorder, other than an autoimmune disorder, after plasma exchange for TTP was begun were excluded.

Table I presents the data for gender and race of the 335 patients in this analysis, divided among eight clinical categories and an additional laboratory category, with comparisons to their appropriate control groups. Table II presents data on the ages of patients within each of the nine patient categories. For three of the categories, there was no significant difference between the patients and control population for the relative frequencies of gender and race: patients with HSCT TMA, women with pregnancy/postpartum-associated TTP, and patients with TTP associated with drugs other than quinine. Gender and/or race disparities were documented in the other six categories.

Among the 25 patients with quinine-associated TTP-HUS, 24 (96%) were women and 24 (96%) were white. The relative frequency of women was significantly different from the control population.

Among the 31 patients with a bloody diarrhea prodrome in whom the suspected etiology was *E. coli* O157:H7 infection [18], 24 (77%) were women and 30 (97%) were white; these relative frequencies were significantly different from their control population.

Among the 29 patients with a previous diagnosis of SLE, 28 (97%) were women and 12 (41%) were black. The predominance of women was not different from a population-based cohort of incident cases of SLE, however the relative frequency of blacks was significantly greater [17]. Among the 20 patients with a previous diagnosis of an autoimmune disorder other than SLE, 9 (45%) were women and 5 (25%) were black. Although the relative frequency of women was not different from the control population, the relative frequency of blacks was significantly greater.

Among the 154 patients with idiopathic TTP, 113 (73%) were women and 40 (26%) were black; these relative frequencies were significantly different from their control population.

Among the 65 patients with severe ADAMTS13 deficiency, 53 (82%) were women and 23 (35%) were black; these relative frequencies were also significantly different from their control population. The 65 patients with severe ADAMTS13 deficiency were in all clinical categories except drug-associated TTP-HUS. Among the 107 idiopathic patients who had ADAMTS13 measurements, the distributions of gender and race were not different between patients with and without severe ADAMTS13 deficiency.

Discussion

Gender and race disparities exist in many diseases and may reflect differences in the etiology, pathogenesis, prevalence, severity, and outcomes [14,15]. During our experience with the Oklahoma TTP-HUS Registry, we have noticed the predominance of women across most of the clinical categories of these syndromes, and also distinctly different race disparities among the different categories. In this study, we have documented that significant gender and/or race disparities occurred in six of the nine categories that were defined for this analysis. The three categories without significant disparities were HSCT-TMA, TTP attributed to drugs other than quinine, and women who were diagnosed with TTP during pregnancy or postpartum. The absence of disparities in these groups of patients may be related to their heterogeneity. The HSCT patients had many different primary disorders; among the 27 patients in the nonquinine drug-associated category, TTP was attributed to 12 different drugs; among the pregnancy/postpartum patients, many may have had severe preeclampsia or the HELLP syndrome rather than TTP [19].

Gender and/or race disparities occurred in the other six categories of patients. In the four categories in which there was a gender disparity, all had a significantly increased relative frequency of women. A race disparity was documented in five categories; in four categories there was a significantly increased relative frequency of blacks; in one there was a significantly increased relative frequency of whites.

Among patients with quinine-associated TTP-HUS, 96% were women and 96% were white. The relative frequency of women, but not the relative frequency of whites, was significantly different from their control population. The cause of TTP-HUS was quinine tablets used for nocturnal leg cramps in 24 patients and tonic water in one patient. The prevalence of nocturnal leg cramps is the same for men and women [20], suggesting that the use of quinine, the common treatment for leg cramps for many years [21], may also be the same for men and women. The common use of quinine for leg cramps in men is supported by data from a survey of 556 US Veterans Administration outpatients (95% men); 56% reported the occurrence of nocturnal leg cramps and quinine was the most commonly used treatment [22]. The predominance of women among patients with quinine-associated TTP-HUS suggests a genetic risk for the development of quinine-dependent antibodies that can cause systemic microvascular thrombosis.

Among patients with TTP-HUS preceded by a prodrome of bloody diarrhea, there were significant disparities of both gender and race; 77% were women and 97% were white. These patients were primarily adults; 5 (16%) of 31 were less than 10-years old; the other 26 were 16 to 82 years old. The increased relative frequency of whites among our patients is the same as among children with diarrhea-associated HUS, who are 95% white [18]. However, the increased relative frequency of women was different from children with diarrhea-associated HUS, in which the frequency of boys and girls is equal [18]. The predominance of whites among both adults and children with diarrhea-associated TTP-HUS suggests a genetic risk for susceptibility to infection with *E. coli* O157:H7 and the effects of Shiga toxin. The gender difference between adults and children with diarrhea-associated TTP-HUS is consistent with the predominance of women in other categories of TTP-

HUS, suggesting a greater risk among adult women for developing systemic microvascular thrombosis.

The increased relative frequency of blacks among patients with a previous diagnosis of SLE or another autoimmune disorder, idiopathic TTP, and patients with severe ADAMTS13 deficiency and the increased relative frequency of women among patients with idiopathic TTP and severe ADAMTS13 deficiency are consistent with an increased risk for autoimmune disorders among blacks and women [17,23].

The strength of these data is the enrollment of all consecutive patients across 21 years from a defined geographic region, without selection or referral bias. Socioeconomic issues or access to care should not be responsible for the gender and race disparities because of the inclusiveness of the Oklahoma Registry, the severity of the TTP-HUS syndromes, the urgent indication for plasma exchange treatment, and its accessibility in the Registry region. A potential limitation is the heterogeneity of the patient groups, which were designated only on the basis of clinical criteria.

The distinct disparities of gender and race among the TTP categories and subgroups may, as in other conditions [14,15], serve as starting points for novel investigations of pathogenesis.

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