

A seasonal association of incident cases of thrombotic thrombocytopenic purpura was not observed in the Oklahoma TTP-HUS Registry

In this issue of **TRANSFUSION**, Park and colleagues¹ describe the seasonal association for all cases of suspected thrombotic thrombocytopenic purpura-hemolytic uremic syndrome (TTP-HUS) treated with plasma exchange (PEX) at the University of North Carolina Healthcare, 1999 to 2008. They report that the occurrence of cases was significantly greater in summer months (June-August) than in fall (September-November) and winter (December-February) for all 97 cases (including relapses) defined as idiopathic TTP and for 54 individual patients with an initial presentation of idiopathic TTP. They also state that more cases occurred in the summer months for all 139 suspected TTP-HUS cases and 31 cases with ADAMTS13 activity of less than 10%.¹ Therefore, we analyzed the seasonal association of patients enrolled in the Oklahoma TTP-HUS Registry. The registry is a population-based inception cohort of all patients for whom PEX treatment is requested for a clinical diagnosis of TTP or HUS.^{2,3} All patients within a defined geographic area, 58 of Oklahoma's 77 counties, are identified because the Oklahoma Blood Institute is the sole provider of PEX for this region.

All 415 consecutive individual patients with an initial episode of clinically diagnosed TTP or HUS identified, 1989 to 2010, were enrolled in the registry. Patients are assigned in a hierarchical order to one of six categories based on the clinical features of their initial episode. A total of 162 patients were described as idiopathic as they did not qualify for one of the five previous categories: stem cell transplantation, pregnancy or postpartum, drug-associated, bloody diarrhea prodrome, or presence of an additional or alternative diagnosis.² ADAMTS13 activity has been measured in the Central Hematology Laboratory of the Inselspital, Berne, Switzerland, by Drs Johanna Kremer Hovinga and Bernhard Lämmle on serum samples collected on 281 (93%) of 301 patients enrolled since November 13, 1995, by two methods: quantitative immunoblotting of plasma-derived von Willebrand factor substrate and a fluorogenic assay using FRETs-VWF73 substrate.³ Severe ADAMTS13 deficiency was defined as less than 10% activity documented by either method.³ To analyze patients identified during complete calendar years, the 67 patients with ADAMTS13

activity of less than 10% from 1996 through 2010 were identified; six patients in whom an alternative diagnosis (systemic infection or malignancy) was discovered to be responsible for their presenting clinical features after PEX had been started were excluded from this analysis. All 61 patients were determined to have acquired severe ADAMTS13 deficiency:³ three patients were postpartum, two presented with bloody diarrhea, three had an additional autoimmune disorder, and 53 were categorized as idiopathic. To determine if the number of incident cases was different across months or seasons, a goodness-of-fit chi-square was calculated; the null hypothesis was that the number of cases was equally distributed across all months or seasons. An alpha of 0.05 was used.

Table 1 demonstrates that the initial presentations of patients in all three analyzed groups were not different across the four seasons. In addition, the initial presentations were also not different across all 12 months: all patients ($p = 0.62$), idiopathic patients ($p = 0.79$), and ADAMTS13-deficient patients ($p = 0.36$). The data for the 61 patients with ADAMTS13 activity of less than 10% are presented in Fig. 1. There was no increased frequency during summer months.

The reason for the difference between the Oklahoma and North Carolina data is not clear. Both states have similar climates. Oklahoma data are based on the initial episodes of all consecutive individual patients from a defined geographic region across 22 years. North Carolina data represent both initial and relapsed episodes as well as multiple episodes for some individual patients. There also may be referral bias of the North Carolina patients. In conclusion, we did not observe a seasonal association of TTP.

CONFLICT OF INTEREST

The authors have no conflict with this topic or these data. JNG serves as a consultant for Baxter, Inc., for development of rADAMTS13 as a potential treatment for TTP and for Alexion, Inc., for development of eculizumab for treatment of aHUS.

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TABLE 1. Seasonal occurrence of initial episodes of patients with TTP-HUS*

Patient category	Season (% of patients)				p value
	Winter	Spring	Summer	Fall	
All patients (415)	27	27	25	22	0.52
Idiopathic patients (162)	28	28	24	20	0.49
Patients with ADAMTS13 activity <10% (61)	23	33	21	23	0.57

* Data are reported as the percent of patients (total number of patients given in parentheses) Seasons are designated as defined by Park et al.¹ A goodness-of-fit chi-square analysis did not reject the null hypothesis that the number of cases was equally distributed across all seasons.

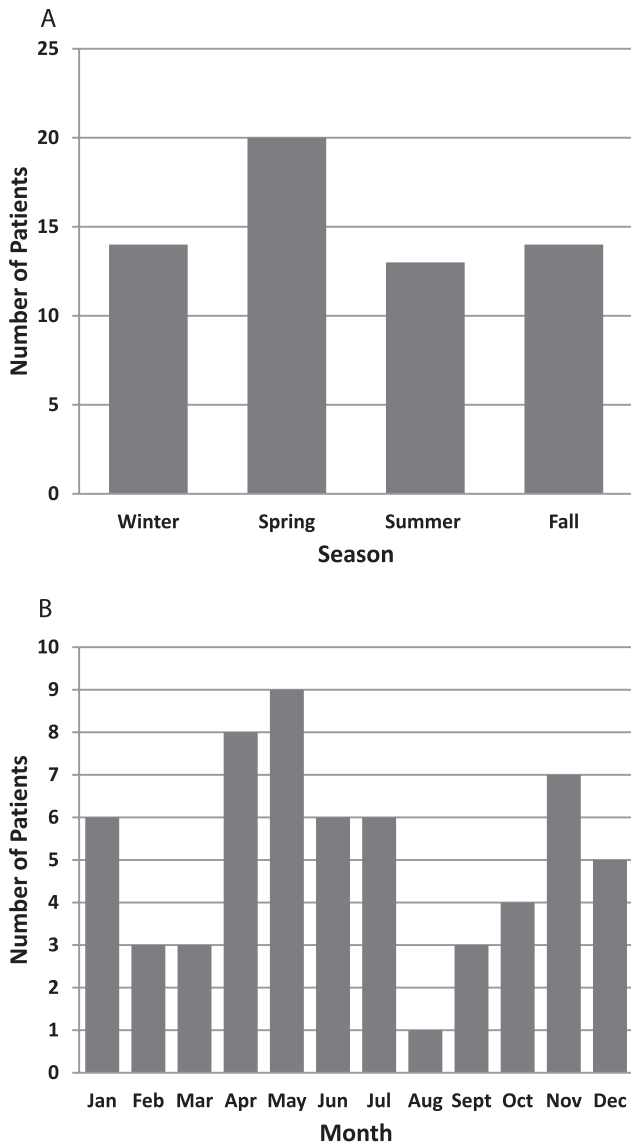


Fig. 1. The number of individual patients among the 61 patients with ADAMTS13 activity of less than 10% who presented with their initial episode of TTP, 1996 to 2010, during the four seasons is presented in (A); the number who presented during each month is presented in (B). A goodness-of-fit chi-square analysis did not reject the null hypothesis that the number of cases was equally distributed across all seasons ($p = 0.57$) and all months ($p = 0.36$).

REFERENCES

1. Park YA, Poisson J, McBee M, Afenyl-Annan A. Seasonal association of thrombotic thrombocytopenic purpura. *Transfusion* 2012;52:1530-4.
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3. Kremer Hovinga JA, Vesely SK, Terrell DR, Lämmle B, George JN. Survival and relapse in patients with thrombotic thrombocytopenic purpura. *Blood* 2010;115:1500-11.

In reply:

We appreciated Drs George and Vesley's letter¹ regarding our article² reporting the seasonal occurrence of thrombotic thrombocytopenic purpura (TTP) at our institution. They did a similar retrospective review of their Oklahoma TTP-HUS registry, which included all patients treated by their group for suspected TTP-HUS on the initial presentation only and found different results.

We focused on all idiopathic TTP cases, both initial and relapse, as defined by the presence of a microangiopathic hemolytic anemia and thrombocytopenia without other explanation. We also examined subpopulations of our patients including initial idiopathic presentations and patients with severe ADAMTS13 deficiency. All of these three groups had a summer predominance of presentation, with the idiopathic and the initial idiopathic groups having a significant difference between summer and fall and winter. We did also investigate the seasonal occurrence of our entire group of patients treated with therapeutic plasma exchange for suspected TTP-HUS and this group again had a summer predominance.

Our findings agree with those of Karimi and colleagues,³ which also showed a summer predominance in their idiopathic TTP population in Iran. Since submitting our article, Hsu and coworkers⁴ reported at the AABB Annual Meeting in San Diego in October 2011 about the seasonal occurrence of TTP at their institution in St Louis, Missouri. They also saw a correlation between increased