High Incidence of Thrombotic Thrombocytopenic Purpura Exacerbation and Relapse Rates Among Patients With Morbid Obesity and Drug Abuse

Preethi Ramachandran MD[1], Burak Erdinc MD[2], Hesham A. Abowaly MD[2], S. Narayanan MD[3], JC Wang MD[1]

1. Brookdale University Hospital and Medical Center, Department of Hematology and Oncology,
2. Brookdale University Hospital and Medical Center, Department of Medicine
3. Southampton University Hospital, NHS Trust, UK

INTRODUCTION

Thrombotic thrombocytopenic purpura (TTP) is a rare disease with high mortality affecting two people per million per year. It is characterized by thrombotic microangiopathy secondary to thrombocyte aggregation caused by ADAMTS13 (a disintegrin and metalloprotease with thrombospondin type 1 repeats, member 13) deficiency [1,2]. ADAMTS13 deficiency can be acquired or congenital. Acquired TTP is primarily caused by autoantibodies leading to accumulation of large vWF multimers causing platelet aggregation and microangiopathic hemolytic anemia (MAHA). TTP classically presents as a pentad: thrombocytopenia, MAHA, kidney injury, neurological involvement and fever. Even though the "classic pentad" is described to help with the diagnosis of the disease, it is neither sensitive nor specific as in our study. Therefore, lack of a full pentad should not be used to exclude the diagnosis. Replenishing ADAMTS 13 and removing the associated antibody by plasma exchange is now the mainstay treatment for TTP patients which can achieve remission in approximately 80% of the cases [3].

SUBJECTS AND METHODS

Chart review of 29 patients who received plasmapheresis at Brookdale University Hospital and Medical Center (Brooklyn, NY) between 2014 to 2020 was performed. Clinical data of our cases were collected from *HYPERSPACE® Epic 2019 Aug*, electronic medical record system by reviewing their demographics, medical history, home medications, presenting symptoms, comorbidities, laboratory parameters, ADAMTS13 level and treatments received. Complete remission was defined as full clinical recovery and recovery of a normal platelet count (>150 x10^9/L) for at least 2 days. Exacerbation was defined as recurrent disease within 30 days after reaching a treatment response. Relapse was defined as recurrent disease 30 days or longer after reaching a treatment response.

TABLES

Table 1: Main characteristics of the patients.

Age, mean ±SD (range)	**47 ±17.73 (22-79)**	
Gender	**n**	**%**
Male	4	36.36%
Female	7	63.63%
Body mass index (BMI), mean ±SD (range)	**35.72 ±13.67 (21.7-59.10)**	
Ethnicity	**n**	**%**
African American	8	72.72%
Hispanic	2	18.18%
Asian	1	9.09%
History of cancer	**1**	**9.09%**
History of Autoimmune Disease	**3**	**27.27%**
Hashimoto thyroiditis	2	18.18%
Anti-phospholipid syndrome	1	9.09%
Drug abuse	**6**	**54.54%**
Cannabinoids	3	27.27%
Opiates	2	18.18%
Benzodiazepines	1	9.09%
PCP	1	9.09%
Methadone	1	9.09%

Table 2: Comparison of Harvard and Oklahoma registries with our study (Brookdale Registry)

	Brookdale Registry	**Oklahoma Registry [2]**	**Harvard Registry [16]**
Geographic region	New York	Oklahoma	Massachusetts
Number of patients	11	78	68
Study population	Clinically suspected cases of TTP with severe ADAMTS13 deficiency	Patients with first the episode of clinically suspected TTP referred for PEX.	Clinically suspected cases of TTP with severe ADAMTS13 deficiency
Threshold for severe ADAMTS13 deficiency	< 10%	< 10%	< 10%
Female, %	63.63%	77%	73.5%
Median age at initial presentation	44	41	40
Ethnic groups	Black, 72.72% Hispanic, 18.18% Asian, 9.09%	White, 62% Black, 36% Native American, 2%	White, 63.6% Black, 19.7% Asian, 1.5% Hispanic, 15.2%
Clinical Findings			
Neurological Involvement, %	54.54%	67%	39.7%
Renal Involvement, %	63.63%	52.5%	-
Fever, %	9.09%	10.0%	35.3%
Laboratory findings			
Hematocrit, %	27.51 (17.1-44.4)	22 (13-28)	27 (23–31)
Platelet count, 9x109/L	20.72 (9-52)	11 (5-63)	17 (12–23)
Serum creatinine, mmol/L	1.63 (0.95-4.7)	1.35 (0.8-5.5)	1.08 (0.78–1.47)
Lactate dehydrogenase, IU/L	4378 (9700-1440)	1500 (274-3909)	1107 (797–1349)
Inhibitor positive, %	90.0%	88%	56%
Exacerbation, %	70.0%	55%	-
Relapse, %	20.0%	44%	-

RESULTS

11 patients were diagnosed with TTP (thrombotic thrombocytopenic purpura) at Brookdale University Hospital and Medical Center between 2014 and 2020. One out of 11 had hereditary form of TTP whereas the rest had acquired TTP. Out of 10 acquired TTP, 9 were newly diagnosed and 1 was relapsed TTP. All patients had low ADAMTS13 activity of <10%. 10 out of 11 had high levels of ADAMTS13 inhibitor levels and one had an undetectable level of inhibitor as the patient had hereditary TTP. The mean age was 47 years and there was a slight female predominance (64%). Majority of our patients were African Americans (72%). Five out of eleven patients were obese (BMI >30 kg/m^2) and four of them were morbidly obese (BMI >40 kg/m^2). Three patients had autoimmune disorders at the time of diagnosis (two patients with Hashimoto's thyroiditis and one with antiphospholipid syndrome). Six patients had positive drug screens which included cannabinoids (3), opiates (2), benzodiazepines (1), PCP (1) and methadone (1). Main characteristics of the patients are summarized in *table 1*. The presenting symptoms on admission were gastrointestinal (63%) neurological (54%), cardiopulmonary (18%).

Classical pentad of TTP was present in only 9% of our patients. Combination of microangiopathic hemolytic anemia and thrombocytopenia was observed in 100%. 63% of patients had acute kidney injury, 54.5% had neurological symptoms and only 9% had fever on admission. Subdural hematoma and acute ischemic stroke was diagnosed in two of the patients who presented with neurological symptoms. AKI was observed in four out of six patients with a positive drug screen and one of those was morbidly obese. All patients with drug abuse and AKI had a complete recovery of their renal function after TTP treatment whereas one patient had only partial improvement due to chronic kidney disease at baseline.

All patients with acquired form of TTP were treated with steroids and plasma exchange. In addition, three of them received immunosuppressive treatment with cyclophosphamide (2) and vincristine (1). One patient with hereditary form of TTP received treatment with plasma infusions rather than plasma exchange. Three patients had a complicated course with systemic infections: *Cytomegalovirus* bacteremia (1), *proteus mirabilis* bacteremia (1) and *group B streptococci* bacteremia (1). On average, patients received 15 sessions of plasma exchange. 70% of acquired TTP patients received rituximab treatment (4.5 doses on average). Complete remission was observed in 80% of our patients (days to remission: 10.5 days, SD 3.93). But unfortunately, exacerbation was seen in 70% of the acquired TTP patients. Exacerbation rates were higher in patients with drug abuse (80%) as well as in those who were morbidly obese (75%). One patient was resistant to plasmapheresis and needed 60 sessions of plasmapheresis in a total of 96 days. Only one out of 9 newly diagnosed acquired TTP had relapsed disease (time of relapse: 3 years). Length of stay was 15 days on average. All patients were discharged home after the initial diagnosis. Three patients died in 3 months, 19

DISCUSSION

TTP can be divided into two categories: first, more commonly seen acquired or autoimmune form (94.5% of cases); second and very rare hereditary form (4.5% of cases) caused by ADAMTS13 biallelic gene mutations also known as Upshaw-Schulman syndrome [4,5]. ADAMTS13 activity levels less than 10% along with clinical features of the disease and laboratory findings are used to make a definitive diagnosis. The main reason for ADAMTS13 deficiency is acquired autoantibodies causing TTP but there may be additional causes which lower the ADAMTS13 levels such as sepsis, cardiac surgery, pancreatitis and liver disease [6-10]. An inhibitory antibody is detected in the majority of the cases [11,12].

African American population was highest among our patient population (73%) compared to *Oklahoma* (36%) and *Harvard registry* (20%), respectively [2,13]. Comparison of our study with both registries are summarized in *table 2*. Complete remission of TTP was observed in 80% of our patients suggesting good response to initial therapy (days to remission: 10.5, SD 3.93). However, we found a very high rate of exacerbations (70%) compared to previous TTP studies including the Oklahoma registry which reported an exacerbation rate of 55% [2,14-19]. Relapse rate is 20% in our patient population compared to 44% in *Oklahoma registry* [2].

Our study group had 36% of morbidly obese (BMI >40 kg/m^2) patients who had significantly lower initial platelet count, high AST and high initial troponin levels compared to the non-morbidly obese patients. Our patients with obesity had high exacerbation (75%) and relapse rates (50%). There is paucity of data on relationship of TTP with obesity [20,21]. Therefore, this association needs to be further evaluated.

The other subgroup of patients who had a high exacerbation rate were patients with a positive drug screen. Four out of five patients (80%) with a history of drug abuse had TTP exacerbations in addition to a high incidence of AKI (66%). It is possible but difficult to prove that these drugs induce the autoimmune reaction of TTP or the causative for increased exacerbation in these patients. Further studies are needed to clarify the relation between drug use and TTP presentation and exacerbation. This may be faced with difficulty due to the rarity of the disease

References

1. Moschcowitz E. An acute febrile pleiochromic anemia with hyaline thrombosis of the terminal arterioles and capillaries: An undescribed disease. Arch Intern Med. 1925;36(1):89-93. doi:10.1001/archinte.1925.00120130092009/2. Page EE, Kremer Hovinga JA, Terrell DR, Vesely SK, George JN. Thrombotic thrombocytopenic purpura: Diagnostic criteria, clinical features, and long-term outcomes from 1995 through 2015. Blood Adv. 2017;1(10):590-600. doi:10.1182/bloodadvances.2017005124/ E. Sadler JE, Moake JL, Miyata T, George JN. Recent advances in thrombotic thrombocytopenic purpura. Hematology Am Soc Hematol Educ Program. 2004:407-423. doi:10.1182/asheducation-2004.1.407/4. Joly BS, Coppo P, Veyradier A. Thrombotic thrombocytopenic purpura. Blood. 2017;129(21):2836-2846. doi:10.1182/blood-2016-10-709857/5. George JN. Congenital thrombotic thrombocytopenic purpura: Lessons for recognition and management of rare syndromes. Pediatr Blood Cancer. 2008;50(5):947-948. doi:10.1002/pbc.21481/6. Mannucci PM, Parolari A, Canciani MT, Alemanni F, Camera M. Opposite changes of ADAMTS-13 and von Willebrand factor after cardiac surgery [7]. J Thromb Haemost. 2005;3(2):397-399. doi:10.1111/j.1538-7836.2005.01115.x/7. Mannucci PO, Canciani MT, Forza I, Lussana F, Lattuada A, Rossi E. Changes in health and disease of the metalloprotease that cleaves von Willebrand factor. Blood. 2001;98(9):2730-2735. doi:10.1182/blood.V98.9.2730/8. George JN. Clinical insights from observations on ADAMTS13 deficiency in liver cirrhosis. Thromb Haemost. 2008;99(6):987-988. doi:10.1160/TH08-05-0278/9. Uemura M, Fujimura Y, Matsumoto M, et al. Comprehensive analysis of ADAMTS13 in patients with liver cirrhosis. Thromb Haemost. 2008;99(6):1019-1029. doi:10.1160/TH08-01-0006/10. Nguyen TC, Liu A, Liu L, et al. Acquired ADAMTS-13 deficiency in pediatric patients with severe sepsis. Haematologica. 2007;92(1):121-124. doi:10.3324/haematol.10262/11. George JN, Nester CM. Syndromes of thrombotic microangiopathy. N Engl J Med. 2014;371(7):654-666. doi:10.1056/NEJMra1312353/12. Scully M, Blombery P. Management of thrombotic thrombocytopenic purpura: current perspectives. J Blood Med. February 2014:15. doi:10.2147/jbm.s46458/13. Bendapudi PK, Li A, Hamdan A, et al. Impact of severe ADAMTS13 deficiency on clinical presentation and outcomes in patients with thrombotic microangiopathies: The experience of the Harvard TMA Research Collaborative. Br J Haematol. 2015;171(5):836-844. doi:10.1111/bjh.13658/14. Froissart A, Buffet M, Veyradier A, et al. Efficacy and safety of first-line rituximab in severe, acquired thrombotic thrombocytopenic purpura with a suboptimal response to plasma exchange. Experience of the French Thrombotic Microangiopathies Reference Center. Crit Care Med. 2012;40(1):104-111. doi:10.1097/CCM.0b013e31822e9d66/15. Page EE, Kremer Hovinga JA, Terrell DR, Vesely SK, George JN. Rituximab reduces risk for relapse in patients with thrombotic thrombocytopenic purpura. Blood. 2016;127(24):3092-3094. doi:10.1182/blood-2016-03-703827/16. Rubia J de la, Moscardó F, Gómez MJ, et al. Efficacy and safety of rituximab in adult patients with idiopathic relapsing or refractory thrombotic thrombocytopenic purpura: Results of a Spanish multicenter study. Transfus Apher Sci. 2010;43(3):299-303. doi:10.1016/j.transci.2010.09.018/17. Ling HT, Field JJ, Blinder MA. Sustained response with rituximab in patients with thrombotic thrombocytopenic purpura: A report of 13 cases and review of the literature. Am J Hematol. 2009;84(7):418-421. doi:10.1002/ajh.21439/18. Jasti S, Coyle T, Gentile T, Rosales L, Poiesz B. Rituximab as an adjunct to plasma exchange in TTP: A report of 12 cases and review of literature. J Clin Apher. 2008;23(5):151-156. doi:10.1002/jca.20172/19. Scully M, Cohen H, Cavenagh J, et al. Remission in acute refractory and relapsing thrombotic thrombocytopenic purpura following rituximab is associated with a reduction in IgG antibodies to ADAMTS-13. Br J Haematol. 2007;136(3):451-461. doi:10.1111/j.1365-2141.2006.06448.x/20. Nicol KK, Shelton BJ, Knovich MA, Owen J. Overweight Individuals Are at Increased Risk for Thrombotic Thrombocytopenic Purpura. Am J Hematol. 2003;74(3):170-174. doi:10.1002/ajh.10418/21. Lombardi AM, Fabris R, Scarda A, et al. Presence of anti-ADAMTS13 antibodies in obesity. Eur J Clin Invest. 2012;42(11):1197-1204. doi:10.1111/j.1365-2362.2012.02710.x