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Prospective registry of adult patients receiving therapeutic plasma exchange with a presumptive diagnosis of thrombotic microangiopathy (TMA): the Turkish hematology research and education group (ThREG)-TMA02 study

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ABSTRACT

Thrombotic microanjiopathy (TMA) is a pathological diagnosis characterized by abnormalities of small vessels leading to microvascular thrombosis of arterioles and capillaries. The current prospective, non-interventional, multicenter study aimed to define the distribution of different TMA forms in adult Turkish patients who were referred for therapeutic plasma exchange (TPE) for presumptive diagnosis of TMA. Patients with serum ADAMTS13 activity <5% were diagnosed as having acquired thrombotic thrombocytopenic purpura (aTTP). Patients presenting with ADAMTS13 activity 6–10 % / normal renal function and patients with ADAMTS13 activity >10 %, normal renal function and no secondary TMA were treated as unclassified TMA. The study included a total of 80 patients (women: 50; man: 30) with a median age of 48 (20−74). Detailed evaluation at 1 month after hospital admission revealed aTTP, secondary TMA, infection/complement-associated hemolytic uremic syndrome and unclassified TMA in 29 (36.2 %), 22 (27.5 %), 23 (28.8 %) and 6 (7.5 %) patients respectively. As subclassification of various TMAs will dictate specific therapy, proper diagnosis in a timely manner is of utmost clinical significance.

1. Introduction

Thrombotic microanjyopathy (TMA) is a pathological diagnosis characterized by abnormalities of small vessels leading to microvascular thrombosis of arterioles and capillaries [1]. Microangiopathic hemolytic anemia and thrombocytopenia (MAHAT) are sine qua non laboratory findings of TMA. On the other hand, there are many disorders and clinical conditions resulting in MAHAT without causing TMA. TMAs are rare but life-threatening disorders. As subclassification of various TMAs will dictate specific therapy, proper diagnosis in a timely manner is of

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utmost clinical significance.

In daily practice it may be very difficult, if not impossible, to differentiate between various TMAs at first presentation. Due to the low specifity of clinical findings and unavailability of ADAMTS13 activity levels at hospital admission, the decision to start or postpone therapeutic plasma exchange for presumptive diagnosis of acquired thrombotic thrombocytopenic purpura (aTTP) may be a real challange for physicians.

A national retrospective TMA registry of Turkey (ThREG-TMA01) has been published in 2017 [2]. The current prospective study aimed to define the distribution of different TMA forms in adult Turkish patients who referred for TPE with a presumptive diagnosis of TMA and is complementary to the aforementioned study.

2. Methods

2.1. Study design

ThREG-TMA02 was a prospective, non-interventional, multicenter study. The primary objective of the study was to define the incidence of atypical hemolytic uremic syndrome (aHUS) among thrombotic microangiopathic (TMA) patients referred for TPE. The secondary objective was the assessment of the demographic, laboratory and clinical characteristics of the study cohort.

2.2. Patients

All consecutive adult (age $\geq$ 18 years) patients who were presented with MAHAT and referred for TPE with a presumptive diagnosis of TMA by participating centers during January 2015-July 2017 period were included in the study. As ADAMTS13 activity is the most important laboratory parameter distinquishing aTTP from other TMAs, patients without available serum samples for measuring ADAMTS13 activity before initiation of TPE were excluded. In all recruited patients serum samples at diagnosis were sent for ADAMTS13 activity and anti-ADAMTS13 antibody assays.

2.3. Terminology

The definition of MAHAT and classification of TMA subtypes were done according to existing consensus reports and the previously published retrospective ThREG-TMA1 study [2–4]. Patients with serum ADAMTS13 activity <5% were diagnosed as aTTP. Neurological impairments were defined either as severe (transient focal abnormalities, seizures, stroke, coma) or minor (headache, transient confusion). Patients with creatinine >1,5 mg/dl or presenting with acute kidney failure (an increase of $\geq$ 0,5 mg/dL of creatinine levels in two successive days or creatinine $\geq$ 4 mg/dL and need for dialysis) were defined as having renal failure. As patients with a presumptive diagnosis of infection-associated hemolytic uremic syndrome could not be confirmed by serology and/or PCR for Shiga toxin expressing bacteria and mutational analysis for genes associated with regulation of alternative complement pathway were unavailable, patients presenting with MAHAT, any sign of renal injury (serum creatinine >1.5 mg/dL, hematuria, oliguria, proteinuria) and ADAMTS13 activity $\geq$5% were classified as infection-associated/complement-mediated hemolytic uremic syndrome (IA/CM-HUS). Patients with an ADAMTS13 activity $\geq$ 5% who had disorders or clinical conditions associated with TMAs are categorized as secondary TMA (sTMA). Patients with the following features were treated as unclassified TMA: 1-ADAMTS13 activity 6–10 % and with normal renal function 2-ADAMTS13 activity >10 %, normal renal function and no secondary TMA. The evaluation and management of patients were done according to the local policy of each participating center. Subclassification of patients was done at first admission before starting TPE and one month later after completion of required tests for differential diagnosis.

2.4. Study oversight

The study was designed as an investigator initiated trial (IIT) and sponsored by Alexion Pharmaceuticals. Data were collected through a web-based electronic database in conjunction with a national research organization (CROTURK). The authors along with the sponsor were involved in study design and had access to the final data. The draft manuscript was prepared by the authors and analyzed by the sponsor before sending for publication. All participants provided written informed consent. The study was approved by central ethics commitee and conducted in line with Declaration of Helsinki.

2.5. Statistics

Descriptive statistics for categorical and quantitative variables were presented as frequency (percentage) and median (min-max), respectively.

3. Results

The study included a total of 95 patients. 12 and 3 patients were excluded from analysis because of unavailable ADAMTS13 activity assessment and a normal platelet count ($\geq$ 150,000/mm^3) at study entry, respectively. The demographic and clinical features of the study cohort are presented in Table 1. The subclassification of TMA was changed in 11 (13.8 %) patients after final evaluation at the first month (Table 2). Ten (12.5 %) patients presented with classic pentad of aTMA, namely microanjiopathic hemolytic anemia, thrombocytopenia, renal failure, fever and neurological abnormalities. 40 (50 %) patients had renal failure at first evaluation, while 27 (33.8 %) patients presented with neurological dysfunction. The distribution of various subtypes of TMAs at study entry and final analysis are presented in Figs. 1 and 2, respectively.

Table 1
Demographic and clinical features of patients cohort.

Total Patients (n)	95
Excluded from analysis (n)	15 ADAMTS13 not evaluated (n: 12) Initial thrombocyte count $\geq$ 150,000/mm^3 (n:3)
Total number of patients used for final analysis (n)	80
Gender (n; %)	Man: 30 (37.5 %)Woman: 50 (62.5 %)
Age (median-range)	48 (20−74)
Fever (n; %)	Yes: 32 (40.0 %)No: 48 (60.0 %)
Neurological Assessment (n; %)	Normal: 53 (66.3 %) Minimal neurologic abnormalities: 21 (26.3 %) Major neurologic abnormalities: 6 (7.5 %)
Renal assessment (n; %)	Renal failure: 40 (50.0 %)Normal: 40 (50.0 %)
Diarrhea (n; %)	11 (13.8 %)
Hgb (g/dL) (median-range)	8,7 (5,3−16,5)
PLT (10^3/mm^3) (median-range)	34.5/mm^3 (4−140/mm^3)
Patients presenting with classic pentad (n; %)	Yes: 10 (12.5 %)No: 70 (87.5 %)
ADAMTS13 activity (n; %)	$\leq$5: 29 (36.3 %)>5: 51 (63.7 %)
Presumptive diagnosis at initial presentation (n; %)	aTTP: 38 (47.5 %) IA/CM-HUS: 22 (27.5 %) Secondary TMA: 20 (25.0 %)
Clinical diagnosis after detailed assessment at 1 month (n; %)	aTTP: 29 (36.2 %) IA/CM-HUS: 23 (28.8 %) Secondary TMA: 22 (27.5 %) Unclassified: 6 (7.5 %)

Table 2
Change in the final diagnosis at 1 month.

INITIAL DIAGNOSIS	DIAGNOSIS AT 1 MONTH
aTTP (n:38)	aTTP (n:28)
	IA/CM-HUS (n:2)
	SECONDARY TMA (n:2)
	UNCLASSIFIED (n:6)
IA/CM-HUS (n: 22)	aTTP (n:0)
	IA/CM-HUS (n:21)
	SECONDARY TMA (n:1)
	UNCLASSIFIED (n:0)
SECONDARY TMA (n: 20)	aTTP (n:0)
	IA/CM-HUS (n:0)
	SECONDARY TMA (n:20)
	UNCLASSIFIED (n:0)
UNCLASSIFIED (n:0)	aTTP (n:0)
	IA/CM-HUS (n:0)
	SECONDARY TMA (n:0)
	UNCLASSIFIED (n:6)

4. Discussion

The distribution of patients presenting with IA/CM-HUS was 22 (27.5 %) and 23 (28.8 %) at first visit and final evaluation at 1 month, respectively. We were not able to discriminate between CM-HUS and IA-TMA due to unavailability of mutation analysis of regulatory proteins in the alternative complement system and serological/PCR analysis of Shiga toxin producing bacteria in patients presenting with diarrhea. Mutational analysis of alternative complement system proteins and Shiga toxin are not evaluated in routine practice. On the other hand, determination of a mutation in the complement system is not required for a diagnosis for aHUS.

The previous TMA studies from Turkey focused mainly on aTTP, reported mostly retrospective/single-center experiences with a relatively limited number of patients and the diagnosis of aTTP relied on clinical judgement without ADAMTS13 evaluation [5–10]. The largest Turkish national retrospective study from 18 centers included all patients who were referred for TPE with a presumptive diagnosis of TMAs and had serum ADAMTS13 activity/anti-ADAMTS13 antibody analysis at diagnosis included a total of 154 patients. 67 (43.5 %), 32 (20.8 %) and 27 (17.5 %) patients were diagnosed as TTP, IA/CM-HUS and sTMA, respectively [2]. There is wide range of subclassification of different TMAs based on demographic features of the study cohort, referral patterns, terminology used for classification of TMAs, inclusion and exclusion criteria used for enrollment of patients. Even in the French CM-HUS registry including 516 patients, the diagnosis of CM-HUS was not required as part of the protocol [11]. According to registry data on TMAs 23–71 %, 25–33 % and 6–33 % of patients were categorized as aTTP, sTMA and CM-HUS, respectively [12–17]. Our findings indicating a 28.8 % incidence of IA/CM-TMA after final evaluation seem to be in line both with our retrospective national experience and international registry data.

TMA is a biopsy finding and nearly all patients with TMA present with MAHAT. Patients with TMA come to medical attention with various clinical presentations. Because signs and symptoms of patients are nonspecific and, tissue biopsy is rarely done in routine practice, the physicians should focus on verification of MAHAT and predicting the possibility of aTTP. As the mortality of aTTP is almost 90 % without TPE, the most important aspect of initial evaluation is to predict significant ADAMTS13 deficiency with basic laboratory parameters. The definition of severe ADAMTS13 activity ranges from 5 to 15% according to different clinical scoring systems in TMA [18]. We used a 5% threshhold for defining severe ADAMTS13 deficiency, but only 3 (3%) patients had ADAMTS13 activity 6–10 % indicating that 5% and 10 % are acceptable threshholds. Recently published guidelines use 10 % for defining severe ADAMTS13 activity but suggest TPE in patients with ADAMTS13 activity in the range of 10–20 % to guide treatment regarding TPE [3,19].

It was remarkable that in only 13.8 % of cases the classification of the TMA subtype changed after final diagnosis at the first month. This point indicates that in most of the scenarios the physicians were able to predict the subtype of TMA at the first clinical presentation, although we are unaware whether participating centers used any clinical scoring system or used just their clinical judgement for predicting the possibility of aTTP.

In daily practice physicians start TPE as soon as possible because aTTP cannot be excluded on clinical grounds alone and had an almost 90 % mortality in the era before TPE. Another relevant problem is accurate diagnosis of CA-HUS. Although CA-HUS is mainly a genetic disorder associated with dysregulated activation of the alternative complement system, neither evaluation of functional status nor genetic mutations frequently encountered in the regulatory proteins of alternative

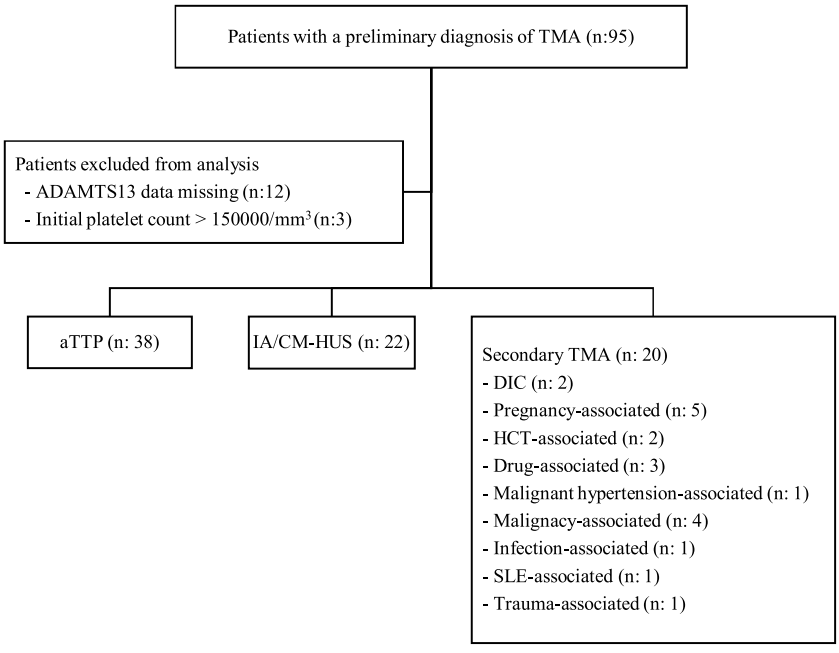

Fig. 1. Subclassification of TMA at study entry.

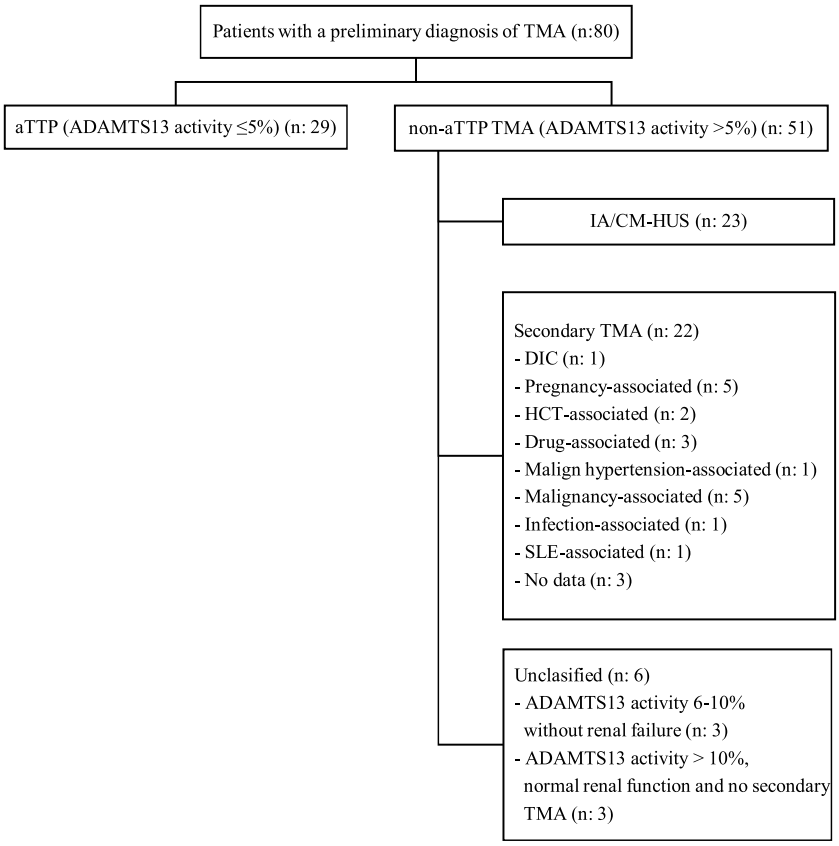

Fig. 2. Subclassification of TMA after final evaluation at 1 month.

complement system, are required for diagnosis and initiation of anti-complement therapy therapy [20]. As complement activation is also observed in various forms of TMAs, it is an ongoing debate whether many clinical conditions are by themselves the reason or just the trigger of a TMA attack in a susceptible individual with inherited or acquired complement activation (CM-HUS) [21]. As of 2021, CM-HUS still remains a clinical diagnosis of exclusion and genetic analysis and/or evaluation of functional status of alternative complement system are not required for diagnosis. But, in order to confirm the genetic background of the disease, to predict prognosis and plan long-term management of the patients and relatives, evaluation of relevant mutaions of the alternative system may be recommended [22].

The pathological background dictates the management of TMAs. The clinical possibilities in a patients with a presumptive diagnosis of aTTP but unresponsive to TPE are refractory aTTP or CM-HUS. As we have effective treatment options for patients presenting with aTTP (TPE) and CM-HUS (eculizumab or ravulizumab) and TPE has important side effects the proper classification of the TMAs is of utmost clinical significance. Anti-complement therapy should be started as soon as possible in patients with low-intermediate probability of aTTP based on clinical scoring systems and unresponsive to five sessions of TPE to prevent chronic renal failure.

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