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Editorial Comment

EDITORIAL COMMENT

An updated classification of thrombotic microangiopathies and treatment of complement gene variant-mediated thrombotic microangiopathy

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ABSTRACT

Conditions presenting with signs of thrombotic microangiopathies (TMAs) comprise a wide spectrum of different diseases. While pathological hallmarks are thrombosis of arterioles and capillaries, clinical signs are mechanical haemolysis, thrombocytopenia and acute renal injury or neurological manifestations. The current classification of various syndromes of TMA is heterogeneous and often does not take the underlying pathophysiology into consideration. Therefore we propose a simplified classification based on the aetiology of different syndromes leading to TMA. We propose to categorize different TMA syndromes in hereditary and acquired forms and classify them based on the genetic background or underlying conditions. Of course, this classification is not always distinctly applicable in each case and from time to time reassessment of the established diagnosis is strongly recommended. The recommended treatment of TMA in the past was plasma exchange (PE). However, recently, the terminal complement inhibitor eculizumab became commercially available and has shown promising results in different open-label studies and case series. In our centre, first-line therapy is PE; however, patients are instantly switched to complement inhibitory therapy in case of treatment failure or intolerance.

Keywords: acute kidney injury, atypical haemolytic uraemic syndrome, complement system, kidney disease, thrombotic microangiopathy

INTRODUCTION

Syndromes presenting with signs of thrombotic microangiopathies (TMAs) encompass a broad group of different diseases, the pathological hallmark of which is arteriolar and capillary thrombosis. Those vascular thromboses then lead to clinical signs of microangiopathic haemolysis, a decrease in platelet count and organ damage. The kidneys and the brain are predominantly affected, but other organs are also frequently involved.

THE CLASSIFICATION OF TMAs

The classification of TMAs in the current literature is often equivocal and somewhat confusing [1–9]. The challenge

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pertaining to this semantic dilemma derives from historical aspects and the evolving understanding of the pathophysiological basis of the different TMA entities, as recently pointed out by Brocklebank *et al.* [3]. Diverging clinical viewpoints of several medical specialities, including paediatricians, haematologists, immunologists and nephrologists, contribute to the pertinent differences in the use of TMA nomenclature (Figure 1).

In his article 'Atypical hemolytic uremic syndrome: a syndrome in need of clarity', Berger [10] recognizes thrombotic thrombocytopenic purpura (TTP) and Shiga-like toxin-producing *Escherichia coli* (STEC)-haemolytic uraemic syndrome (HUS) as distinct disease entities. However, all other TMA syndromes are summarized as atypical HUS (aHUS), either primary or secondary. We suggest a modification of the classification of Brocklebank *et al.* [3] (which is based on the terminology introduced by Nester and George [1]), who use the term primary TMA including hereditary [aHUS with complement gene mutations; TTP with *ADAMTS13* mutations; Cobalamin C deficiency–mediated TMA; diaycylglycerol kinase ε (*DGKE*) TMA] and acquired [TTP with ADAMTS13 autoantibody; aHUS with complement factor H (CFH) autoantibodies] TMAs. The two other groups of TMAs proposed by Brocklebank *et al.* [3] comprise a large group of secondary TMAs (*de novo* TMA after solid organ transplantation; TMA after bone marrow transplantation; drug-induced TMA; TMA with severe hypertension; TMA with autoimmune conditions; pregnancy-associated TMA; haemolysis, elevated liver enzymes, low platelet count syndrome; TMA with glomerular disease; malignancy-associated TMA) and infection-associated TMAs (STEC-HUS (Shiga-Toxin Producing *Escherichia coli* associated HUS); pneumococcal HUS; human immunodeficiency virus (HIV)–associated TMA; other infections) [3].

In line with the aforementioned classification of TMA, we use the term hereditary TMA for TMAs with a genetic cause [complement gene variant TMA (previously aHUS), *ADAMTS13* variant TMA (previously TTP), *DGKE* variant TMA, plasminogen (*PLG*) variant TMA, thrombomodulin (*THBD*) variant TMA]. The second group comprises acquired forms of TMA, as shown in Figure 2. The classification shown in this figure considers the overlap between hereditary and acquired TMAs, as hereditary TMAs may require a trigger factor and acquired TMAs may also have a genetic background. However, if the disease occurs in a patient with a known pathogenic or likely pathogenic genetic variant, we classify the disease as hereditary. Until recently, the identified genes involved in the pathogenesis of complement gene variant TMA (cTMA) were *CFH*, *CFI*, *CFB*, C3, *THBD*, *PLG* and *CD46*. However, now vitronectin (an inhibitor of the terminal complement complex formation) was recently identified as a genetic risk factor for cTMA by Bu *et al.* [11].

We also prefer to include STEC-HUS and other infectious disease-related TMAs in the group of acquired TMAs. This is in contrast to other classifications that, in our opinion, describe STEC-HUS as a separate/primary TMA or HUS entity based on the history and not on the pathophysiology of an underlying infection.

We use the term unexplained TMA and include, as suggested by Brocklebank *et al.* [3], treatment-responsive or non-responsive TMA, which should also include plasma therapy (Table 1).

TREATMENT OF cTMA

Historically the standard treatment of cTMA is based on the substitution of complement regulatory proteins and/or the removal of anti-complement autoantibodies by either plasma infusion (PI) or plasma exchange (PE). Plasma therapy is recommended to be initiated within 24 h of initial disease presentation. Ideally PE is commenced as soon as possible after presentation and performed daily for 5 days, followed by five sessions per week for 2 weeks and three sessions per week thereafter. The ideal duration of PE is unknown and the decision must be guided by the patient's clinical response and condition [12]. The aim is to exchange a plasma volume of 40 mL/kg of body weight, which sums to ∼1–1.5 times the total plasma volume. In the acute setting, PI should only be considered if PE is not immediately available. If maintenance therapy is needed, then the treatment can be performed using either PI or PE. However, the ideal treatment intervals need to be determined individually for each patient.

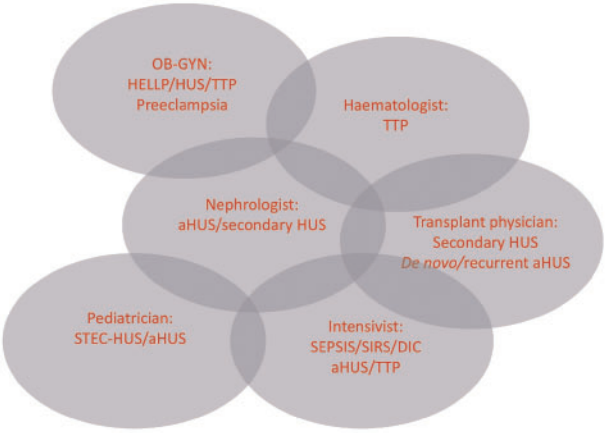

FIGURE 1: Different medical specialities are involved in the diagnosis and therapy of TMA syndromes (using traditional classification of TMAs). OB-GYN, obstetrics–gynaecology; HELLP, haemolysis, elevated liver enzymes, low platelet count; HUS, haemolytic uremic syndrome; TTP, thrombotic thrombocytopenic purpura; aHUS, atypical haemolytic uremic syndrome; STEC-HUS, Shiga-toxin producing *E. coli* associated HUS; SIRS, systemic inflammatory response syndrome; DIC, disseminated intravascular coagulation.

Generally, response rates to PE vary between 30% and 80% depending on the underlying genetic disease background. However, haematological response (i.e. normalization of haemoglobin levels or platelet count) is more common than renal response (i.e. decrease of serum creatinine). The most common complications of plasma-based therapies include allergic reactions, hypotension and complications related to the central venous access [13–15].

In recent years, eculizumab has become available as a therapy for cTMA. Eculizumab is a humanized antibody against the complement protein C5 and inhibits the terminal common pathway of the complement cascade. Subsequently this prevents the formation of the membrane attack complex [16]. Open-label studies in patients with a presumed hereditary cTMA have shown promising results, but no randomized trials are yet available, and prospectively followed cohorts have been compared against historical cohorts [17]. Treatment with eculizumab consists of weekly infusions of 900 mg for the first 4 weeks, followed by administration of 1200 mg every second week. Currently the ideal treatment duration is debated, as current guidelines advise lifelong therapy in all patients. This poses an enormous financial burden since eculizumab is one of the most expensive drugs on the market. Interestingly, published data suggest that lifelong therapy might not be necessary in all patients, as eculizumab has been safely discontinued in

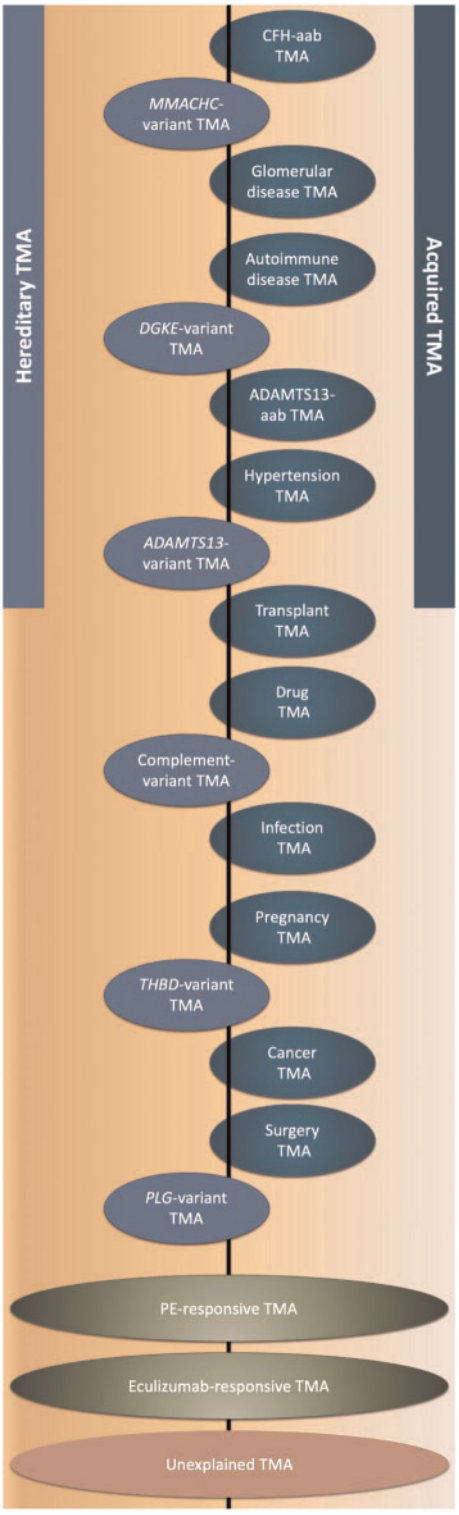

FIGURE 2: Classification of TMA syndromes according to aetiology. Two major groups include hereditary TMAs and acquired TMAs, with some overlap between hereditary and acquired TMAs. Hereditary TMAs may require a trigger factor, whereas acquired TMAs may also have a genetic background. Colour coding: blue: hereditary; petrol blue: acquired; green: response to therapy; red: unclear disease entity. ADAMTS13, a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13; MMACHC, methylmalonic aciduria and homocystinuria type C protein; Aab, autoantibody; TMA, thrombotic microangiopathy; DGKE, diacylglycerol kinase epsilon; MMACHC, Methylmalonic aciduria and homocystinuria type C protein; PLG, plasminogen; THBD, thrombomodulin; CFH, complement factor H; PE, plasma exchange.

patients in Dutch and Italian cohorts [18, 19]. The optimal surveillance after the cessation of eculizumab therapy needs to be studied in greater detail [2]. The most prominent risks of the treatment include the development of meningococcal infections, immune-mediated drug reactions, the possibility of developing neutralizing antibodies and the potential of hepatotoxicity [18]. In general, patients need to be vaccinated against *Neisseria meningitides* serogroups A, C, W, Y and B prior to therapy initiation or, alternatively, prophylactically treated with antibiotics until 2 weeks after the vaccination. Notably, failure of the first vaccination to provide sufficient immunization has been reported and therefore antibiotic prophylaxis seems pivotal, as fatal infections with the germ have been reported even after vaccination [20, 21].

In case of acquired types of TMA (other than anti-CFH antibody-mediated TMA), the management must focus on resolving the underlying condition suspected to cause TMA. If treatment of the suspected responsible condition does not resolve TMA, then a hereditary type of TMA may be considered and treated accordingly.

THE VIENNA APPROACH TO THE TREATMENT OF COMPLEMENT-MEDIATED TMA

In our centre, the first-line therapy for suspected cTMA is PE. Treatment is performed daily for the first 3 days and then extended to every other day until clinical response allows for a further extension of treatment intervals and eventually cessation of treatment. In some patients, maintenance PE may be necessary. Overall treatment duration is determined based on the patient's response and clinical condition.

In case of treatment failure (persistent haemolysis and/or renal impairment after at least five sessions of PE) or intolerance, eculizumab is started following the recommended dosing scheme of the manufacturer. The treatment duration of eculizumab therapy is individually determined for each patient based on the clinical history (i.e. hereditary cTMA with a positive family history, kidney transplant recipient) and risk factors for disease recurrence (i.e. genetic disease background). In the past, we successfully weaned patients after long-term eculizumab treatment, following a report from Ardissino *et al.* [19]. Importantly, close monitoring is extremely important in such cases, besides appropriate counselling of patients. However, such reports are anecdotal and the safety of applied cessation protocols needs to be investigated. In our experience, ∼45% of cTMA patients partially responded to PE, while 36% experienced a full response and 80% of the partial responders experienced a full recovery under therapy with eculizumab.

We have formerly used PI as prophylactic therapy in stable pregnant cTMA patients and observed excellent maternal and foetal outcomes in the majority of followed pregnancies [22]. Again, these protocols lack systematic safety evaluations. Similarly, we successfully applied our prophylactic PE/PI protocol in cTMA patients receiving kidney transplants [23].

CONCLUSION

The diagnosis and classification of syndromes of TMA remain a challenge, as a uniform classification has not existed until now. Proposed different classifications are either not focused on the underlying pathophysiology or are overly complicated. That is why we propose a new approach towards a classification based on the aetiology of TMA syndromes (Figure 2).

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Table 1. Differences in classification of TMAs

Reference	Categories	Subcategories	Classification
	Hereditary TMA	Complement variant TMA	Classification based on pathophysiological considerations and triggering factors
		ADAMTS13 variant TMA	
		DGKE variant TMA	
		MMACHC variant TMA	
	Acquired TMA	Surgery TMA, transplant TMA	
		Drug TMA	
		Infection TMA	
		Pregnancy TMA	
		Cancer TMA	
		Glomerular disease TMA, autoimmune disease TMA	
		CFH-aab TMA, ADAMTS13-aab TMA	
Berger [10]	Complement-mediated aHUS	Primary dysregulation	Classification based on clinical presentation and type of complement dysregulation
		Secondary dysregulation	
	Non-complement-mediated aHUS	DGKE, cobalamin C	
Brocklebank *et al.* [3]	Primary TMA: hereditary	aHUS with compelement gene mutation	Classification into primary (genetic + autoantibody mediated) and secondary TMA with the introduction of overlaps between the different categories and introduction of the category 'unexplained' TMA
		TTP with *ADAMTS13* gene mutation	
		DGKE-TMA	
		cblC deficiency-mediated TMA	
	Primary TMA: acquired	aHUS with FH autoantibody	
		TTP with ADAMTS13 autoantibody	
	Secondary TMA	Pregnancy-associated TMA, HELLP	
		TMA with severe hypertension	
		De novo TMA after SOT, TMA after BMT	
		Drug-induced TMA	
		TMA with glomerular diseases/autoimmune conditions	
		Malignancy-associated TMA	
	Infection-associated TMA	STEC-HUS, pneumococcal HUS	
		HIV-associated TMA	
		Other infections	
	Unexplained TMA	NA	

MMACHC, methylmalonic aciduria and homocystinuria type C protein; CFH-aab, complement factor H autoantibodies; ADAMTS13-aab, ADAMTS13 autoantibodies; cblC, cobalamin C; HELLP, haemolysis, elevated liver enzymes, low platelet count; SOT, solid organ transplantation; BMT, bone marrow transplantation; TMA, thrombotic microangiopathy; aHUS, atypical haemolytic uremic syndrome; HIV, human immunodeficiency virus.

The treatment of syndromes of TMA have historically focused on PE. In our centre, PE comprises the first-line therapy for TMA, and only in case of treatment failure or intolerance do we switch to complement inhibitory therapy.

CONFLICT OF INTEREST STATEMENT

M.G. and C.A. have received travel and congress funding from Alexion and C.A. has worked as a subinvestigator on an Alexion-sponsored study.

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