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Review article

Atypical hemolytic uremic syndrome and thrombotic thrombocytopenic purpura: Clinically differentiating the thrombotic microangiopathies

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ABSTRACT

The increased understanding of the pathophysiology of both atypical hemolytic uremic syndrome (aHUS) and thrombotic thrombocytopenic purpura (TTP) in recent years has led to significant therapeutic advances for both conditions. These advances have placed an increased emphasis on a more rapid differentiation of both disorders which remain clinical diagnoses. In particular, recent data demonstrating the effectiveness of complement inhibition in patients with aHUS have increased the need for a more rapid and accurate differentiation of aHUS and TTP. Previously utilized criteria have used the presence or absence of neurologic or renal injury and the pretreatment ADAMTS13 activity to differentiate aHUS from TTP. The use of presenting clinical symptoms and findings alone to differentiate these conditions is problematic given their overlapping clinical presentations. Similarly, the use of the pretreatment ADAMTS13 activity alone to differentiate aHUS from TTP is also problematic, and could lead to the inappropriate witholding of plasma exchange (PEX) therapy. However, when used collectively, the pretreatment clinical findings (symptoms and laboratory data) and ADAMTS13 activity in the context of the patient's response to PEX therapy can allow for a more effective differentiation of these two disorders in a timely fashion that will allow for the prompt initiation of the most appropriate therapy.

1. Introduction

Historically there have been numerous debates in the medical literature attempting to accurately diagnose and differentiate thrombotic thrombocytopenic purpura (TTP) and atypical hemolytic uremic syndrome (aHUS). Differentiating features of the two disorders that have been proposed previously suggested that the presence or severity of clinical symptoms including renal and neurologic injury can differentiate these two rare thrombotic microangiopathies. More recently following the discovery of the ADAMTS13 protease, it had been proposed that a severe deficiency (<5% or <10%) of the ADAMTS13 protease may correctly differentiate TTP from aHUS [1–4]. However, despite these apparent advances in our ability to differentiate these conditions, the results of the debate were largely academic as plasma-based therapy was considered the first-line therapy for both disorders.

This all changed however after the report regarding the effectiveness of eculizumab in a child with a diagnosis aHUS by Gruppo et al. [5]. Despite plasma-based therapy that had been effective previously, hematologic abnormalities persisted and renal function worsened. The initiation of eculizumab therapy resulted in hematologic improvement, but more importantly improvement in renal function. Soon thereafter prospective studies of eculizumab in patients with a clinical diagnosis of aHUS were completed that resulted in the approval of eculizumab for the treatment of aHUS by the European Medicines Agency and the Federal Drug Administration (FDA) of the United States [6,7]. These remarkable data have forced investigators to re-examine how to more accurately differentiate aHUS from TTP to allow for the prompt initiation of the most appropriate therapy for both disorders. There are certainly challenges though given that there is no objective diagnostic test to differentiate these disorders at the time of initial presentation. Both aHUS and TTP remain clinical diagnoses. The text that follows will review both the historic and more recent data regarding the use of the clinical presentation, ADAMTS13 activity, and the clinical laboratory studies that collectively may provide a framework for a more accurate differentiation of aHUS from TTP and allow for the prompt initiation of the most appropriate therapy for patients with aHUS.

2. Clinical diagnosis and the impact on published studies

The finding of a microangiopathic hemolytic anemia and thrombocytopenia, with or without end organ injury should alert the clinician to the possible diagnosis of a thrombotic microangiopathy (TMA) that may require the rapid initiation of PEX therapy. Historically physicians have used the findings of renal injury and neurologic abnormalities to differentiate aHUS from TTP. While to some extent

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this dogma may have been partially correct (more prominent renal injury in patients with aHUS), the reliance on clinical symptoms alone does not accurately differentiate these two disorders and should not be relied upon [8].

Much of the difficulty with the published data that attempted to differentiate these two disorders stems from the inherent fallibility in applying clinical criteria to separate disorders that have overlapping presentations. This is especially true in the studies that attempted to determine the rates of severe ADAMTS13 deficiency seen in patients with aHUS or TTP. Depending upon the clinical definition used to define each disorder, the incidence of a particular finding could be relatively increased or decreased. This will always be the case when there are no objective diagnostic criteria to define each disorder.

To avoid these potential pitfalls in this manuscript, data to be presented regarding TTP will be limited to reports from studies in which the data were analyzed in the context of the severely deficient ADAMTS13 activity at presentation. This is not meant to imply that the finding of severely deficient ADAMTS13 activity is diagnostic of acquired TTP, nor to say that non-deficient ADAMTS13 activity excludes the diagnosis, but rather to identify a homogenous population of TTP patients from which objective conclusions may be drawn. These same issues are present as well with the diagnosis of aHUS, and to a greater extent given the lack of any single objective diagnostic marker that can be reliably used to define aHUS patients. For this reason whenever possible, the criteria used to define the diagnosis of aHUS in any referenced study will be stated.

3. Neurologic injury and the differentiation of atypical hemolytic uremic syndrome and thrombotic thrombocytopenic purpura

Neurologic injury is a common finding at presentation in patients with TTP. In patients with a diagnosis of TTP and severely deficient ADAMTS13 activity, neurologic injury has been reported in 25%–79% of patients at presentation [9–13]. While there may be some subjectivity in the specific definition, these data support the relatively common finding of neurologic abnormalities in TTP patients. A recent report however from Coppo et al. from the French TMA registry demonstrated that the rate of CNS involvement in TMA patients was not significantly different in the ADAMTS13 deficient and non-deficient patients. If severely deficient ADAMTS13 activity in a TMA patient is used as a surrogate definition for the diagnosis of TTP, these data would suggest that rates of neurologic injury are not significantly different in TTP patients versus TMAs from other etiologies [14].

It is accepted that aHUS is a disorder with end-organ damage that primarily targets the kidney, but extrarenal involvement including neurologic injury has been reported in 10–30% of patients [15,16]. In recent years, a better understanding of aHUS as a disorder of complement dysregulation, coupled with the ability to more easily obtain complement control protein mutation analysis have been able to provide confirmation that neurologic injury can be seen in patients with aHUS. As a disorder of complement dysregulation, it is certainly plausible that there could be neurologic injury in a disease characterized by widespread complement-mediated microvascular injury. Proof of this hypothesis has come from recent case reports that have demonstrated profound neurologic injury in patients with a TMA and documented mutations of complement regulatory proteins [16–18]. In a more striking case, Salem et al. reported the case of a 66 year-old female with a clinical diagnosis of aHUS, with renal failure and profound neurologic injury that did not respond to PEX therapy. The diagnosis of aHUS was confirmed by the documentation of a mutation of C3 and the subsequent complete recovery after therapy with eculizumab [19]. It is for these reasons that the presence or absence of neurologic findings or injury at presentation alone cannot be used to differentiate TTP from aHUS.

4. Renal injury and the differentiation of atypical hemolytic uremic syndrome and thrombotic thrombocytopenic purpura

As with neurologic injury previously, it has also been suggested that severe renal injury is isolated to the diagnosis of aHUS, and may be used to differentiate aHUS from TTP. While renal failure that requires hemodialysis during the acute presentation is one of the prominent findings that favors a diagnosis of aHUS over TTP, renal injury severe enough to require hemodialysis may still be seen in patients with TTP mediated by a severe deficiency of the ADAMTS13 protease. In the report by Hovinga et al., 10% of TTP patients with severely deficient ADAMTS13 activity were found to have acute renal failure (increasing serum creatinine for 2 consecutive days or increased serum creatinine and requiring hemodialysis within 7 days of diagnosis) [20]. Similarly, as initially reported by Coppo et al., renal failure requiring hemodialysis in patients with ADAMTS13 deficient TTP was less common than in the cohort of patients with ADAMTS13 activity >5% (9.7% vs. 46.7%), but it still occurred in 3/31 patients [10]. A recent update of the data from the French TMA Registry also showed that end-stage renal disease was also significantly more common in the ADAMTS13 detectable group than the ADAMTS13 deficient group (21% vs. 0%, $p < 0.0001$) [14]. In contrast, data from Zheng et al. was consistent with the report from our institution demonstrating that renal failure at presentation requiring hemodialysis was not seen in patients with severely deficient ADAMTS13 activity, but was restricted to TMA patients with detectable ADAMTS13 activity [9,21]. These data support the hypothesis that severe renal injury requiring hemodialysis is more common in patients with TMAs with detectable ADAMTS13 activity, but this criteria cannot be used alone to differentiate TTP from other TMAs given that acute renal failure can rarely be seen in ADAMTS13 deficient TTP.

5. ADAMTS13 activity and the differentiation of atypical hemolytic uremic syndrome and thrombotic thrombocytopenic purpura

Beginning with the discovery of the ADAMTS13 protease [3,22], there was hope that the ADAMTS13 activity could be used to objectively differentiate TTP from aHUS. And while initial reports suggested that this may be the case [2–4] (Table 1), a closer look at the studies and their reliance on the clinical differentiation of the cohorts of TTP and aHUS reveals the potential fallibility of relying on the ADAMTS13 activity alone to differentiate these two TMAs [8,23].

Veyradier et al. reported in 2001 a greater frequency of a deficiency of the von Willebrand factor (VWF) cleaving protease in patients with TTP compared to those with HUS (89% vs. 13%) [2]. While these data seem encouraging, the difficulties arise in the fact that the clinical definition of TTP or HUS was dependent upon the classification of the referring site. With the rates of VWF protease deficiency dependent upon the clinical classification, and without clear and objective criteria to clinically define TTP vs. aHUS, the results of this study and the rates of respective vWF protease deficiency could be significantly affected by the differing criteria used by the referring sites. Similarly, the ADAMTS13 activity in 127 patients clinically classified as TTP was reported by Tsai et al. to all have severely deficient ADAMTS13 activity [3,4]. Assumptions made though to clinically classify patients as

Table 1
Reported rates of severely deficient ADAMTS13 activity in patients clinically diagnosed with aHUS or TTP across different studies.

	Number of patients	Patients with severe ADAMTS13 deficiency	
Clinical categorization	aHUS/TTP	aHUS	TTP
Veyradier et al. [2]	45/66	13%	89%
Remuzzi et al. [23]	9/12	55%	92%
Tsai et al. [3,4]	NA/127	NA	100%

NA, not applicable.

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