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Understanding thrombotic microangiopathies in children

Bérangère S. Joly^{1,2}, X. Long Zheng³, and Agnès Veyradier^{1,2,*}

¹Service d'hématologie biologique and EA3518-Institut universitaire d'hématologie, Groupe Hospitalier Saint Louis-Lariboisière Assistance Publique - Hôpitaux de Paris, Université Paris Diderot, Paris, France.

²French National Reference Centre for Thrombotic MicroAngiopathies, Assistance Publique – Hôpitaux de Paris, Paris, France.

³Division of Laboratory Medicine, Department of Pathology, The University of Alabama at Birmingham, Birmingham, AL 35249, USA.

Thrombotic microangiopathy (TMA) is an ultra-rare syndrome. The incidence in children is estimated to be ~ 3.0 cases/10⁶ population per year (Fig. 1). Very importantly, TMA belongs to the Thrombocytopenia Associated- Multi Organ Failure (TAMOF) syndromes and, therefore, its diagnosis should be considered in critically-ill children. Thus, intensive care physicians and nurses should be familiar with this rare but specific cause of TAMOF. TMA is life-threatening, resulting from ischemic multiorgan failure and characterised by its diversity and high ICU mortality rate, ~ 20%, despite appropriate treatment [1, 2]. The common features for TMA are microangiopathic haemolytic anemia (haemolysis, elevated lactate dehydrogenase, reduced haptoglobin, and fragmentation of red blood cells) and thrombocytopenia. Organ injury, associated with disseminated thrombi in the microcirculation, further supports the diagnosis of TMA. Differential diagnosis includes idiopathic thrombocytopenic purpura (ITP), Evans syndrome or malignancy-associated haematological abnormalities, in which organ injury is uncommon. Also, in contrast to disseminated intravascular coagulation (DIC), TMA are usually associated with normal prothrombin time (PT), activated partial thromboplastin time (aPTT), factor V and fibrinogen. Despite overlapping clinical and biological features, TMA has its distinct pathophysiology and therapeutic management [3]. The most frequent TMA syndromes reported in children are haemolytic uraemic syndrome (HUS), in which renal impairment is the prominent clinical feature. Thrombotic thrombocytopenic purpura (TTP), another TMA syndrome, also occurs in children, often associated with cerebral involvement. Secondary TMA are defined as TMA occurring with other comorbidities serving as the triggering events. These include severe infections, autoimmunity, haematopoietic progenitor cells or solid organ transplantations, malignancy and drugs. Therefore, the diagnosis of secondary TMA can be extremely challenging [1]. In this review, HUS and TTP will be discussed in more detail.

*Correspondence: agnes.veyradier@aphp.fr.

Conflicts of interest

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Childhood Haemolytic Uraemic Syndrome.

Several types of HUS have been proposed. An infection-associated HUS is caused by Shiga-toxin-producing *Escherichia coli* (STEC) strain and *Streptococcus pneumoniae*. STEC-HUS (~ 80–90% of HUS) usually occurs 5–10 days after a gastrointestinal infection (*E. coli* serotype O157:H7 or O104:H4, mainly) and a prodrome bloody diarrhoea; it is caused after haemorrhagic colitis and microvascular damage where the toxin enters circulation.

Streptococcus pneumoniae-associated HUS (~ 5% of HUS), suspected after a history of pulmonary infection or meningitis, is due to the production of a neuraminidase responsible for cleaving the sialic acid of glycoproteins that exposes the cryptic Thomsen-Friedenreich antigen. Atypical HUS (aHUS) (~ 5–10% of HUS) is mainly caused by an uncontrolled activation of the complement through the alternative pathway resulting from mutations in the genes encoding complement factor H (CFH), complement factor I (CFI), complement factor B (CFB), membrane cofactor protein (MCP), C3, and thrombomodulin (THBD), and autoantibodies against CFH or CFI [4, 5]. Very rarely, aHUS is due to mutation in diacylglycerol kinase ϵ (*DGKE*) or deficiency of cobalamin C (cbl-C) [6, 7]. The clinical presentation of aHUS is highly variable, but severe renal impairment is still the predominant feature.

Treatment of HUS depends on its aetiology and pathophysiological mechanisms. Treatment of STEC-HUS is largely supportive, including aggressive hydration and dialysis, with the aim to preserve renal function. However, in patients with neurological symptoms, plasma therapy (infusion of fresh frozen plasma or plasma exchange) may be considered. Recovery of STEC-HUS is usually spontaneous and the outcome is generally excellent [4, 6]. Antibiotics (amoxicillin or third-generation cephalosporin) are needed in *Streptococcus pneumoniae*-HUS. aHUS is a recurrent disease associated with poor outcomes if not treated promptly. Genetic investigations are not required to initiate treatment [8]. Once STEC-HUS (stool culture or identification of shigatoxin), *Streptococcus pneumoniae*-HUS (in a proper clinical context) and TTP (normal ADAMTS13 activity) diagnosis are excluded, a monoclonal anti-C5 antibody (eculizumab) that blocks the activation of C5 should be considered as early as possible [9]. Plasma exchange is reserved for patients with autoantibodies against CFH or CFI. The time required to obtain the results of the biological investigations (usually a few days) should not delay plasma therapy. While plasma exchange is still used in many centres for HUS, it alone does not halt the progress of end-stage renal disease and requirement for renal transplantation, despite the improvement of haematological parameters [10]. The risk of anti-complement therapy includes meningococcal disease. Therefore, there is a longer-term risk of severe bacterial infection for which preventative strategies including immunisations and/or prophylactic antibiotics may be necessary in children prior to or receiving eculizumab therapy. Parenteral administration of hydroxo-cobalamin, folinic acid or betaine are the treatments of choice for aHUS associated with cbl-C deficiency [1].

Childhood Thrombotic Thrombocytopenic Purpura.

This is also an ultra-rare disease (less than 10% of all TTP cases) [11, 12]. TTP is primarily caused by a severe deficiency of plasma ADAMTS13 activity (< 10 IU/dL). Severe

deficiency of ADAMTS13 activity results in an accumulation of ultralarge von Willebrand factor (VWF) multimers, which leads to disseminated platelet-rich thrombi in the microcirculation [11–14]. Severe ADAMTS13 deficiency in childhood TTP is primarily caused by mutations of *ADAMTS13* (congenital TTP) [15] or by autoantibodies against ADAMTS13 (autoimmune TTP) [11–14]. TTP patients may present similar signs and symptoms as HUS patients, but they may have more severe thrombocytopenia (platelet count is usually less than $30 \times 10^9/L$) and a relatively normal serum creatinine (< 1.7 – 2.0 mg/dL). Also, the differential diagnosis of secondary TTP from idiopathic cases can be extremely challenging in some cases [16, 17].

In patients with autoimmune TTP, daily therapeutic plasma exchange is the treatment of choice to remove autoantibodies and supply normal ADAMTS 13 [18]. In patients with congenital TTP, prophylactic plasma infusions (~ 10 – 15 mL/kg body weight bi-weekly) is required to prevent chronic TTP relapses and consecutive organ ischemia [18]. Recombinant ADAMTS13 is hopefully making its way as a novel therapy in the near future [19]. Treatment should continue until normalisation of platelet counts ($> 150 \times 10^9/L$) and serum lactate dehydrogenase (LDH) for two consecutive days, with a resolution of clinical signs and symptoms. For autoimmune TTP, corticosteroids and rituximab (anti-CD20 monoclonal antibody) should be prescribed early to accelerate the recovery and reduce relapses [16, 18]. Other immunosuppressive strategies including cyclophosphamide, mycophenolate mofetil, azathioprine, and splenectomy are reserved to TTP patients with more refractory disease [18]. Long-term follow-up with periodical assessment of plasma ADAMTS13 activity, evaluation of autoimmunity, organ sequelae, and quality of life is crucial for management of paediatric patients with TTP [16,18].

We conclude that childhood TMA syndromes have many pathophysiological and clinical features in common. They have their own unique causes and therapeutic management strategies. While clinical signs and symptoms are overlapping between TTP and HUS, severe deficiency of plasma ADAMTS13 activity (< 10 IU/dL) is diagnostic for TTP in a proper clinical context. Plasma infusion or exchange is the treatment of choice for congenital or autoimmune TTP. To date, aHUS remains a diagnostic exclusion. Low serum levels of C3 and C5 may only be seen in 20% of aHUS patients; therefore, normal complement levels do not exclude the diagnosis of aHUS. Eculizumab is the only effective therapy available for aHUS resulting from overwhelming complement activation. Plasma therapy was also used in the past for aHUS, but it did not show its long-term efficacy. Genetic tests are not required for initial diagnosis and management of aHUS, but the results may be helpful in predicting future relapse, particularly in patients requiring renal transplantation. Renal transplantation is curative for patients with MCP mutations, but not for those with CFH and CFI or C3 mutations due to their liver production.

References

1. George JN, Nester CM (2014) Syndromes of thrombotic microangiopathy. *N Engl J Med* 371:654–666 [PubMed: 25119611]
2. George JN, Al-Nouri ZL (2012) Diagnostic and therapeutic challenges in the thrombotic thrombocytopenic purpura and hemolytic uremic syndromes. *Am Soc Hematol Educ Progr* 2012:604–609

3. Moake JL (2002) Thrombotic microangiopathies. *N Engl J Med* 347:589–600 [PubMed: 12192020]
4. Scully M, Cataland S, Coppo P et al. (2017) Consensus on the standardization of terminology in thrombotic thrombocytopenic purpura and related thrombotic microangiopathies. *J Thromb Haemost* 15:312–322 [PubMed: 27868334]
5. Noris M, Remuzzi G (2009) Atypical hemolytic-uremic syndrome. *N Engl J Med* 361:1676–1687 [PubMed: 19846853]
6. Fakhouri F, Zuber J, Frémeaux-Bacchi V et al. (2017) Haemolytic uraemic syndrome. *Lancet* 390:681–696 [PubMed: 28242109]
7. Grangé S, Bekri S, Artaud-Macari E et al. (2015) Adult-onset renal thrombotic microangiopathy and pulmonary arterial hypertension in cobalamin C deficiency. *Lancet* 386:1011–1012 [PubMed: 26369474]
8. Zuber J, Fakhouri F, Roumenina LT et al. (2012) Use of eculizumab for atypical haemolytic uraemic syndrome and C3 glomerulopathies. *Nat Rev Nephrol* 8:643–657 [PubMed: 23026949]
9. Licht C, Ardissino G, Ariceta G et al. (2015) The global aHUS registry: methodology and initial patient characteristics. *BMC Nephrol* 16:207 [PubMed: 26654630]
10. Noris M, Caprioli J, Bresin E et al. (2010) Relative role of genetic complement abnormalities in sporadic and familial aHUS and their impact on clinical phenotype. *Clin J Am Soc Nephrol* 5:1844–1859 [PubMed: 20595690]
11. Joly BS, Coppo P, Veyradier A (2017) Thrombotic thrombocytopenic purpura. *Blood* 129:2836–2846 [PubMed: 28416507]
12. Saha M, McDaniel JK, Zheng XL (2017) Thrombotic thrombocytopenic purpura: pathogenesis, diagnosis and potential novel therapies. *J Thromb Haemost* 15:1889–1900 [PubMed: 28662310]
13. Furlan M, Robles R, Galbusera M et al. (1998) von Willebrand factor-cleaving protease in thrombotic thrombocytopenic purpura and the hemolytic-uremic syndrome. *N Engl J Med* 339:1578–1584 [PubMed: 9828245]
14. Tsai HM, Lian EC (1998) Antibodies to von Willebrand factor-cleaving protease in acute thrombotic thrombocytopenic purpura. *N Engl J Med* 339:1585–1594 [PubMed: 9828246]
15. Levy GG, Nichols WC, Lian EC et al. (2001) Mutations in a member of the ADAMTS gene family cause thrombotic thrombocytopenic purpura. *Nature* 413:488–494 [PubMed: 11586351]
16. Joly BS, Stepanian A, Leblanc T et al. (2016) Child-onset and adolescent-onset acquired thrombotic thrombocytopenic purpura with severe ADAMTS13 deficiency: a cohort study of the French national registry for thrombotic microangiopathy. *Lancet Haematol* 3:e537–e546 [PubMed: 27720178]
17. Reese JA, Muthurajah DS, Kremer Hovinga JA et al. (2013) Children and adults with thrombotic thrombocytopenic purpura associated with severe, acquired Adamts13 deficiency: comparison of incidence, demographic and clinical features. *Pediatr Blood Cancer* 60:1676–1682 [PubMed: 23729372]
18. Joly BS, Vanhoorelbeke K, Veyradier A (2017) Understanding therapeutic targets in thrombotic thrombocytopenic purpura. *Intensive Care Med*. 10.1007/s00134-016-4662-3
19. Scully M, Knöbl P, Kentouche K et al. (2017) Recombinant human ADAMTS-13: first in human study evaluating pharmacokinetics, safety and tolerability in cTTP patients. *Blood* 130:2055–2063 [PubMed: 28912376]

Fig. 1.

Incidence of child-onset thrombotic microangiopathy syndromes. Haemolytic uraemic syndrome (*HUS*) and thrombotic thrombocytopenic purpura (*TTP*) are the most frequent thrombotic microangiopathy (TMA) reported in children. HUS includes either infection-induced HUS (Shiga-toxin-producing *Escherichia coli* (*STEC-HUS*) and *Streptococcus pneumoniae*) or atypical HUS (aHUS) (dysregulation of the complement alternative pathway, mutation of *DGKE* (diacylglycerol kinase ϵ) and cobalamin C (cbl-C) defect). TTP pathophysiology is based on both inherited (congenital TTP) or acquired deficiency (autoimmune TTP) of ADAMTS13. All incidences are expressed as the number of new cases per 10⁶ children (< 18 years old) per year, except for aHUS (*) the incidence of which is provided for both adults and children