Journal of Thrombosis and Circulation Open Access

Li W, J Thrombo Cir 2018, 4:2
DOI: 10.4172/2572-9462.1000e112

Editorial Open Access

Diagnosing Thrombotic Microangiopathy: A Challenging Clinical Situation

Li W*

Department of Pathology and Laboratory Medicine, Children's Mercy Hospital, University of Missouri-Kansas City School of Medicine, Kansas City, USA

***Corresponding author:** Weijie Li, Assistant Professor, Department of Pathology and Laboratory Medicine, Children's Mercy Hospital, University of Missouri-Kansas City School of Medicine, 2401 Gillham Rd, Kansas City, MO 64108, USA, Tel: +816-760-8816; E-mail: wli@cmh.edu

Received date: April 11, 2018; **Accepted date:** April 26, 2018; **Published date:** April 27, 2018

Citation: Li (2018) Diagnosing Thrombotic Microangiopathy: A Challenging Clinical Situation. J Thrombo Cir 4: e112. doi:10.4172/2572-9462.1000e112

Editorial

Thrombotic microangiopathy (TMA) refers to a pathophysiologic process leading to systemic thrombosis involving small vessels, which results in microangiopathic hemolytic anemia (MAHA), thrombocytopenia and organ damage [1-3]. There are many causes of TMA [1-3]. Prompt identification of the underlying etiology is critical because a delay in diagnosis and subsequent treatment can be life-threatening.

Thrombotic thrombocytopenic purpura (TTP) and hemolytic uremic syndrome (HUS) are two well-established TMA syndromes [3-5]. TTP is caused by a severe deficiency in ADAMTS13 (A Disintegrin and Metalloprotease with ThromboSpondin type 1 motif, member 13), a metalloprotease that cleaves von Willebrand factor multimers. The deficiency is either autoantibody mediated (acquired TTP, mostly in adults) or due to autosome recessive ADAMTS-13 gene mutations (congenital TTP, mostly in neonates or young children). The mainstay therapy is therapeutic plasma exchange (TPE) for acquired TTP or plasma infusion for congenital TTP. HUS is defined by the triad of MAHA, thrombocytopenia and acute kidney injury. Approximately 90% of the patients develop it after infection by Shiga-like toxin producing *Escherichia coli* (STEC). STEC-HUS is also called typical HUS and most commonly seen in children. STEC-HUS is mainly managed by supportive care [6,7]. The HUS cases not related to Shiga toxin are called atypical HUS (aHUS), which occurs in all age groups and can be secondary to a variety of medical conditions. Primary aHUS is related to the dysregulation of alternative complement system, so that it is also called complement related HUS. A genetic deficiency in one or more of the complement regulatory proteins is commonly seen in these patients. Primary aHUS is mainly treated with eculizumab, a humanized complement C5 monoantibody, with or without TPE [6-8].

Since the clinical manifestations of these disorders are similar or overlap with each other, the diagnosis can be very challanging without the application of proper laboratory tests. Actually the laboratory tests assessing the key molecules involved in their pathogeneses play a paramount role in the diagnosis. A stepwise diagnostic model generated based on recent publications is shown in Figure 1. Of course, from a practical point of view, multiple tests may need to be performed at the same time to avoid the delay of the diagnosis, and TPE may initiate immediately instead of waiting for the results.

Clinical diagnosis of TMA will be made when a patient presents with increased schistocytes (>1% RBCs), non-immune (Coombs-) hemolytic anemia (low hemoglobin, elevated lactate dehydrogenase, low haptoglobin), thrombocytopenia, and evidence of organ damage. Then the first step is to screen for secondary HUS with underlying conditions including infection caused by agents other than STEC (*Streptococcus pneumonia*, HIV and H1N1 influenza A, etc.), malignancy, drugs, bone marrow or solid organ transplantation, pregnancy (HELLP or preeclampsia), malignant hypertension, glomerulopathies, systemic diseases (systemic lupus erythematous, antiphospholipid syndrome and scleroderma). The presence of coagulopathy points to DIC immediately. There is no specific treatment for HUS in these patients except treating the underlying conditions. Therefore, secondary HUS should be carefully screened based on clinical information and the available laboratory tests to avoid unnecessary treatment [3,4,6-8].

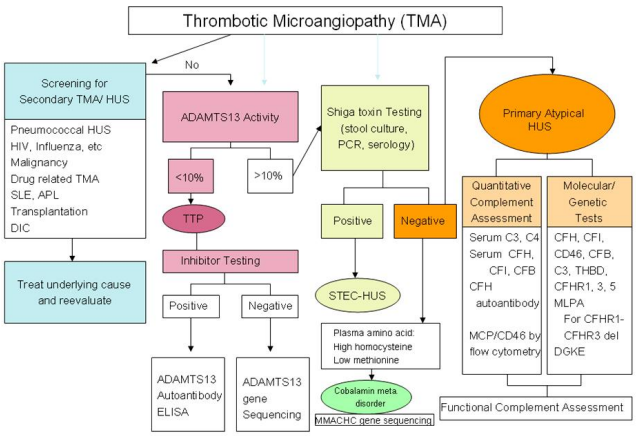

Figure 1: Diagnostic algorithm for thrombotic microangiopathies (TMAs). Abbreviations: TTP, thrombotic thrombocytopenic purpura; HUS, hemolytic uremic syndrome; SLE, systemic lupus erythematous; APL, antiphospholipid syndrome; DIC, disseminated intravascular coagulation; STEC, Shiga toxin producing Escherichia coli; CFH, factor H; CFI, factor I; CFB, factor B; MCP, membrane cofactor protein; THBD, thrombomodulin; CFHR, CFH related gene; MLPA, multiplex ligation dependent probe amplification; DGKE, diacylglycerol kinase ε; MMACHC, methylmalonic aciduria and homocystinuria type C protein.

If there are no aforesaid underlying conditions identified, ADAMS13 activity should be tested. The diagnosis of TTP will be established if ADAMS13 activity is less than 10% and will be followed by the tests for ADAMS13 inhibitor and autoantibody. ADAMS13 gene sequencing should be performed if there is no ADAMS13 inhibitor present. A recently proposed TTP prediction tool, PLASMIC score, using basic lab results (platelet count, MCV, INR, creatinine, bilirubin, reticulocyte count) and clinical information seems to have a good

predictive value for severe ADAMS13 deficiency [9]. If ADAMS13 activity is over 10%, TTP can be ruled out, and the diagnosis of HUS will be made. Stool culture, serology test and/or molecular test for STEC are needed to confirm the diagnosis of typical HUS. Primary aHUS will be diagnosed if there is no evidence of Shiga-like toxin or Shiga toxin [3-8].

For all primary aHUS patients, complement study including quantitative, functional and genetic tests should be performed. Low C3, low CFB and normal C4 plasma level indicate complement alternative pathway activation. The normal plasma levels of complement proteins do not exclude the complement abnormality with dysregulation. Genetic study is necessary in all primary aHUS cases. Since over 10% of the patients have mutations in two or more complement regulators, and some have anti-CFH antibody in addition to a gene mutation, the detection of a mutation or anti-CFH antibody does not preclude the necessity to study all genes. Approximately 20% of pedigrees show an autosomal recessive or dominant mode of inheritance. Since the penetrance of this disease is low (around 50%), it is very difficult to predict the risk of developing the disease in family members carrying the same mutation as their proband [3-8]. A rare cause of TMA, cobalamin metabolism disorder, should be tested if there is no evidenced of complement abnormality [10].

Since the results of some laboratory tests, esp., molecular tests may not be available for days or even weeks, immediate management plan has to be made based on clinical information. Age can help narrow down the differential diagnosis. In patients less than 6 months old, complement related aHUS is most common, pneumococcal HUS needs to be considered, so do congenital TTP and cobalamin metabolism disorder. In patients aged from 6 months to 5 years, STEC-HUS is most common, complement related HUS comes next, pneumococcal HUS is also possible. In preadolescents and adolescents, aHUSs, esp., MCP-HUS and anti-CFH antibody-HUS are common, so is acquired TTP [8]. Besides age, other clinical information favoring aHUS over typical HUS includes insidious onset, relapse, history of unexplained anemia, recurrent HUS after kidney transplantation. Please be aware that the presence of CNS injury or severe kidney damage is not specific for TTP or HUS respectively, nor is the presence of diarrhea for STEC -HUS [3-5].

In summary, TMAs are life-threatening conditions that often need immediate diagnosis and subsequent proper treatment. Diagnosing TMAs can be very challenging. Thanks to the progress in understanding the pathogenesis of these conditions, laboratory tests assessing the key molecules have been established. With the availability of these tests and following proper diagnostic strategy, the diagnosis of TMA can be straightforward.

References

1. Moake JL (2002) Thrombotic microangiopathies. N Engl J Med 347: 589-600.
2. Zheng XL, Sadler JE (2008) Pathogenesis of thrombotic microangiopathies. Annu Rev Pathol 3: 249-277.
3. Scully M, Cataland S, Coppo P, de la Rubia J, Friedman KD, et al. (2017) Consensus on the standardization of terminology in thrombotic thrombocytopenic purpura and related thrombotic microangiopathies. J Thromb Haemost 15: 312-322.
4. Scully M, Hunt BJ, Benjamin S, Liesner R, Rose P, et al. (2012) Guidelines on the diagnosis and management of thrombotic thrombocytopenic purpura and other thrombotic microangiopathies. Br J Haematol 158: 323-335.
5. Shatzel JJ, Taylor JA (2017) Syndromes of thrombotic microangiopathy. Med Clin North Am 101: 395-415.
6. Sawai T, Nangaku M, Ashida A, Fujimaru R, Hataya H,et al. (2014) Diagnostic criteria for atypical hemolytic uremic syndrome proposed by the Joint Committee of the Japanese Society of nephrology and the Japan Pediatric Society. Pediatr Int 56: 1-5
7. Jokiranta TS (2017) HUS and atypical HUS. Blood 129: 2847-2856.
8. Ariceta G, Besbas N, Johnson S, Karpman D, Landau D, et al. (2009) Guideline for the investigation and initial therapy of diarrhea-negative hemolytic uremic syndrome. Pediatr Nephrol 24: 687-696.
9. Bendapudi PK, Hurwitz S, Fry A, Marques MB, Waldo SW (2017) Derivation and external validation of the PLASMIC score for rapid assessment of adults with thrombotic microangiopathies: A cohort study. Lancet Haematol 4: e157-e164.
10. Sharma AP, Greenberg CR, Prasad AN, Prasad C (2007) Hemolytic uremic syndrome (HUS) secondary to cobalamin C (cblC) disorder. Pediatr Nephrol 22: 2097-2103.