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Consensus statement

Diagnostic and therapeutic guidelines of thrombotic microangiopathies of the Spanish Apheresis Group☆

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ABSTRACT

Thrombotic microangiopathies (TMA) are disorders defined by the presence of a microangiopathic hemolytic anaemia (with the characteristic hallmark of schistocytes in the peripheral blood smear), thrombocytopenia and organ malfunction of variable intensity. Thrombotic thrombocytopenic purpura and hemolytic uraemic syndrome are the most important forms of TMA and, without the adequate treatment, they are associated with high morbimortality. In recent years, significant advances in the knowledge of the pathophysiology of TMA have occurred. Those advances have allowed us to move from a syndromic diagnosis with a similar treatment to all entities to the search of etiologic diagnosis which would lead to a specific treatment, finally leading to a better outcome of the patient. This document pretends to summarise the current status of knowledge of the pathophysiology of TMA and the therapeutic options available, and to offer a diagnostic and therapeutic practical tool to the professionals caring for the patients.

Guía diagnóstica y terapéutica de las microangiopatías trombóticas del Grupo Español de Aféresis

Palabras clave:
Microangiopatía trombótica
Púrpura trombocitopénica trombótica
Síndrome urémico hemolítico
Aféresis
Recambios plasmáticos

RESUMEN

Las microangiopatías trombóticas (MAT) son un grupo de entidades que se caracterizan por presentar una anaemia hemolítica microangiopática (con los típicos esquistocitos en el frotis de sangre periférica), trombocitopenia y afectación de órganos de intensidad variable. La púrpura trombocitopénica trombótica y el síndrome urémico hemolítico son las formas más importantes de MAT, y sin el tratamiento adecuado se asocian a una elevada morbimortalidad. En los últimos años se han producido avances notables en el conocimiento de la fisiopatología de las MAT. Estos avances nos han permitido pasar de un diagnóstico sindrómico con un tratamiento similar en todos los casos, a buscar un diagnóstico etiológico y un tratamiento acorde a la etiología que ha conllevado una mejoría en el pronóstico de los pacientes. Este documento pretende resumir el estado actual del conocimiento de la fisiopatología y las opciones terapéuticas disponibles, y también presentar a los profesionales que tratan a este tipo de pacientes una aproximación diagnóstica y terapéutica práctica.

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Introduction

In the last few years, thrombotic microangiopathies (TMAs) have probably been one of the medical fields with the most important changes in the knowledge we have about both their physiopathology and treatment. In fact, in almost 90 years we have gone from the first description by Eli Moschcowitz in 1925 of a disease that had not been described up to that moment and that he attributed to a "potent venom with agglutinative and haemolytic effects"[1] to being able to specify the mutation that causes congenital forms of thrombotic thrombocytopenic purpura (TTP) or developing peptide inhibitors of C3 activation[2] to treat the hyperactivation of the complement seen in atypical haemolytic-uraemic syndrome (aHUS).

Due to this recent fast progresses in the knowledge and treatment of TMAs, the Spanish Aphaeresis Group from the Spanish Society of Haematology and Haemotherapy and the Spanish Society of Blood Transfusion and Cellular Therapy decided to form a working group to publish a guideline that would summarise the current conditions for the diagnosis and treatment of this type of diseases.

The guideline authors believe the study will be useful for the specialists who treat this type of diseases and will help them through the complex process of diagnosing and treating patients with a TMA.

Definition and epidemiology

TMAs are a group of diseases that produce alterations in the vascular endothelium, with peripheral blood smear findings typical of a microangiopathic haemolytic anaemia (schistocytes), characteristic laboratory data (an increase in reticulocytes and lactate dehydrogenase [LDH] levels) and thrombocytopenia of varied acuteness.

The list of TMA-associated diseases is wide (Table 1). The most important diseases within TMAs are TTP, both congenital and acquired (autoimmune), typical HUS associated with Shiga toxin-producing *Escherichia coli (E. coli)* infections (HUS associated with diarrhoea or STEC-HUS) and aHUS. Both TTP and the different varieties of HUS are rare diseases. In medical literature, little more than 100 cases of congenital TTP (Upshaw–Schulman syndrome) have been published, and its exact incidence and prevalence are unknown, although they are probably underestimated. It is more common in infants and adolescents, but it can emerge at any age. The annual incidence of autoimmune TTP is estimated at about 4–6 new cases per million inhabitants in the U.S.A.[3] and at 6 cases per million inhabitants in the United Kingdom,[4] but there is no reliable data about Spain. It has a maximum peak of incidence in the fourth decade of life, with a slight predominance in women (3:2) and black people. Table 2 shows the incidence of TTP gathered in the TMA Japanese record.[5]

The annual incidence of STEC-HUS is of around 2 cases per 100,000 inhabitants in adults and of 6 cases per 100,000 children under the age of 5. aHUS represents approximately 5% of the HUS and can emerge at any age, but there is a special predominance in children and young adults. It is considered an exceptionally rare disease, and its incidence in the U.S.A. is of 1–2 cases/million inhabitants in people of up to 18 years of age, with no conclusive data about the adult population,[6] whereas in Europe its incidence is estimated at 0.11 cases/million inhabitants. However, we can anticipate that a better knowledge of the physiopathology of these diseases will come along with an increased number of diagnosed patients in the near future (Table 3).

The development of a TMA can emerge associated with different disorders or drugs; these are called secondary TMAs (Table 2).[5]

Classification of thrombotic microangiopathies. Aetiology and physiopathology

Thrombotic thrombocytopenic purpura

Both congenital and autoimmune or acquired forms emerge as a result of a deficiency or dysfunction of a protein referred to as a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13 (ADAMTS13), in charge of splitting von Willebrand's factor (vWF). It was identified in 1996,[7,8] but it was not until 2001 that it was called ADAMTS13, after determining its structure and verifying its homology with other members of the ADAMTS[9] metalloprotease family.

Under physiological conditions, the vWF is released by endothelial cells and stays adhered to the surface of the cell. The metalloprotease ADAMTS13 targets the A2 domain of vWF splitting the ultra-large multimers that have high platelet affinity. Then, the vWF is released into the bloodstream with a configuration that does

Table 1
Thrombotic microangiopathies classification.

Primary thrombotic microangiopathies	
Disease	Pathophysiology
Infection-induced HUS	*Escherichia coli* O157:H7 strain and other strains that are not O157:H7, *Shigella dysenteriae* type 1, *Staphylococcus pneumoniae* (neuraminidase)
aHUS	Genetic alterations of the complement: CFH, MPC, CFI, THBD, CFB and C3 mutations. Immune alterations of the complement: anti-CFH antibodies.
Idiopathic TTP	Immune ADAMTS13 alterations (activity <5–10%) with inhibitor antibodies
Congenital TTP (Upshaw-Schulman syndrome)	Genetic ADAMTS13 alterations (activity <5–10%) without inhibitor antibodies
Secondary thrombotic microangiopathies	
Type of trigger	
Drugs	Quinine, mitomycin C, gemcitabine, cisplatin, interferon, VEGF and tyrosine kinase inhibitors, ticlopidine, clopidogrel, calcineurin inhibitors (cyclosporine, tacrolimus), sirolimus, valacyclovir, oral contraceptives
Connective tissue diseases	SLE; antiphospholipid syndrome; scleroderma
Pregnancy	HELLP, preeclampsia
Others	HIV-related infection; glomerulopathies; malignant hypertension; H1N1 (influenza A); neoplasias; methylmalonic acidemia with homocystinuria; HSCT, SOT

CFB: complement factor B; CFH: complement factor H; CFI: complement factor I; HELLP: haemolytic anaemia, elevated liver enzymes and low platelet count; SLE: systemic lupus erythematosus; MCP: membrane cofactor protein; TTP: thrombotic thrombocytopenic purpura; HUS: haemolytic-uraemic syndrome; aHUS: atypical haemolytic-uraemic syndrome; THBD: thrombomodulin; SOT: solid organ transplantation; HSCT: haematopoietic stem cell transplantation; VEGF *vascular endothelial growth factor*; HIV: human immunodeficiency virus.