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REVIEW ARTICLE

Thrombotic thrombocytopenic purpura

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Abstract Thrombotic thrombocytopenic purpura (TTP) is a disease with a high rate of mortality if a proper treatment is not instated. Plasmapheresis with plasmatic exchange is the treatment of choice. Diagnosis is performed demonstrating microangiopathic hemolytic anemia, a negative direct Coombs test and thrombocytopenia. Among the clinical data, neurological and renal alterations stand out. When there is a reasonable suspicion in the diagnosis, plasmapheresis must be initiated immediately. There are different diseases that may be similar to the TTP signs and symptoms, especially in pregnant women. TTP has a high risk of relapse and may leave sequelae.

Introduction

Eli Moschowitz was the first to describe TTP, when performing the autopsy of a 16-year-old girl whom he had treated. During this autopsy, Moschowitz found hyaline thrombi occluding the arterioles and capillaries, he later described them as ''aggregated platelets''.[1] The presence of hemolytic anemia, negative Coombs, schistocytes, thrombocytopenia, and high lactate dehydrogenase (LDH) in patients with neurological and/or renal alterations[9] strongly suggests a TTP diagnosis.

TTP has a mortality rate of 90% without treatment.[2] The first attempts to reduce mortality involved large doses of steroids.[3] The following attempt included the use of fresh blood.[4] Undoubtedly, the turning point in TTP treatment was the use of plasma, which first took place in 1977.[5] One of the greatest progresses concerning the comprehension of the physiopathology of this disease was to identify the unusually long von Willebrand factors multimers,[6] and later, to identify the deficiency of the protease in charge of splitting this multimers in congenital TTP,[7] and lastly, to identify that protease as the thirteenth member of the ADAMTS family (a disintegrin and metalloproteinase with thrombospondin-1 repeats).[8]

Definition

Thrombotic thrombocytopenic purpura (TTP) is a pathology which puts the patient's life in danger, with a mortality rate

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of over 90% when a plasmapheresis with plasmatic exchange treatment is not instated. It may affect multiple systems and organs, the nervous system being the one that is usually the most affected. Secondly, it affects the renal function due to the microthrombus occluding the microvasculature. It is clinically characterized by two main laboratory alterations: thrombocytopenia and microangiopathic hemolytic anemia. Direct Coombs test results are negative and LDH is invariably increased.

Etiology

TTP is classified according to its etiology (Chart 1), although TTP can be congenital, as a result of a mutation of the gene responsible for desynthesizing ADAMTS13.[10] The most common form of TTP is idiopathic or autoimmune, where antibodies directed against ADAMTS13 are created.[11]

Pregnancy is among the causes of TTP, even though diagnosis in these cases is complicated because the clinical and laboratory findings are very similar to pregnancy-related syndromes like preeclampsia and the HELLP syndrome. In the case of TTP, the signs and symptoms are more severe and the quantification of ADAMS-13 is useful, since in other pathologies it is usually normal.[12] Some medications have been linked to the appearance of TTP, quinine being the main responsible.[13] Clopidogrel, ticlopidine, cyclosporine A and mitomycin C, among others, have also been linked as TTP triggers.[14]

Chemotherapy, hematopoietic stem cell transplants, HIV, and lupus are factors frequently related to TTP. They are, however, poorly understood. Hematopoietic stem cell post-transplant TTP is linked to the use of cyclosporine A and is usually a severe clinical picture, and it is difficult to make the patient enter remission.[15,16]

Epidemiology

Young women are more prone to this disease. In 2005, there was a study published reporting the incidence of TTP and hemolytic uremic syndrome (HUS), using records which included all patients sequentially for whom plasmapheresis treatment is requested by the Oklahoma Blood Institute due to clinical suspicion of TTP or HUS, based on the presence of microangiopathic hemolytic anemia and thrombocytopenia without an apparent etiology.

The incidence rate for all patients with clinical suspicion of TTP-HUS in the Oklahoma records was 11.29 per million inhabitants. The incidence rate for idiopathic TTP-HUS patients was 4.6 per million inhabitants, and the incidence rate for patients with severe ADAMTS13 deficiency was 1.74 per million inhabitants.

The incidence rate of TTP associated with severe ADAMTS13 deficiency is over 9 times higher in black people than other races. The incidence rate of TTP-HUS comparing women with men was >1.[17]

Physiopathology

The main histological finding in TTP is hyaline thrombi, formed by platelet aggregation. These thrombi are responsible for capillary occlusion, with the subsequent ischemia in different organs.[1,18]

Table 1 Classification of TTP.

Type	Trigger
Congenital (Upshaw–Shulman syndrome)	Mutation in the gene responsible for synthesizing ADAMTS13.
Acquired or idiopathic	Autoantibodies against ADAMTS13.
Related to pregnancy	
Drug-related	Clopidogrel, ticlopidine.
HIV-related	
Related to chemotherapy	Cyclosporin A, mitomycin C.
Related to hematopoietic stem cell transplant	Associated with the use of cyclosporin A

The von Willebrand Factor (vWF) plays a key role in platelet aggregation. VWF produced exclusively in endothelial cells and platelets, is stored as Wiebel-Palade granule in endothelial cells and as α-granule in platelets. Within these granules it is stored in an ultra-large shape (ULvWF).[7] After being secreted, ULvWF attaches to the endothelial surface. The longer the vWF is, the greater the effect on platelet aggregation, because it is more related to the platelet's Ib receptor. The role of ADAMTS13 is to split the ULvWF into smallest molecules.[9,19] In congenital TTP, ADAMTS13 activity may be lower than 5%, due to mutations in the gene responsible for ADAMTS13 production.[10] Regarding idiopathic TTP, findings show that it is an autoimmune process, mediated by IgG-class antibodies.[11] Even though ADAMTS13 deficiency is suggested as the main culprit, it is important to mention the fact that other causes have been studied, such as lymphocytes, macrophageactivation, high IL-1, IL-6, IL-2 and TNF-α levels, and transforming growth factor (TGF)-β, among others.[20,21]

Signs, symptoms and laboratory findings

Classically, a pentad is described, consisting of thrombocytopenia, microangiopathic hemolytic anemia, fever, neurological symptoms and renal dysfunction.[2] It is worth stressing that currently this pentad is rarely seen, since treatment with plasmapheresis is instated before it occurs. Nowadays, the only thing required is thrombocytopenia and microangiopathic hemolytic anemia in order to establish diagnosis, and, as mentioned above, the presence of schistocytes, a negative direct Coombs and a high LDH confirm clinical suspicion of TTP (Tables 1 and 2).

Clinical findings which pave the way to thrombocytopenia suspicion are epistaxis, menorrhagia, hematuria, gingivorrhagia, etc. Nevertheless, significant hemorrhage data is not necessarily found, as in the case of autoimmune thrombocytopenic purpura. Platelets are below normal levels, typically less than 20×10^9/L. Lab work shows hemoglobin below normal levels, elevated reticulocytes, elevated indirect bilirubin, elevated LDH, low haptoglobin, normal coagulation time, usually in early stages of the disease, and a negative Coombs direct test can also be used. In a peripheral