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STRATEGIC TOOLS FOR DIAGNOSING ATYPICAL HAEMOLYTIC URAEMIC SYNDROME IN A VARIETY OF THROMBOTIC MICROANGIOPATHY. II: DIFERENTIAL DIAGNOSIS AND TREATMENT.

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RESUMEN:

El Sindrome Urémico Hemolítico Atípico (SHU a), Púrpura Trombótica Trombocitopénica (PTT), Síndrome Úrémico Hemolítico secundario a la toxina Shiga de la Escherichia Coli (SHU -STEC), Síndrome antifosfolipídico y otras microagiopatías trombóticas (TMA) tales como como las vistas en: Esclerosis Sistémica Progresiva, Lupus Eritematoso, Virus de la Inmunodeficiencia Humana, Preeclampsia, Síndrome HELLP, algunas drogas, trasplante de Células Madre tienen formas clínicas similares de presentación y anormalidades de laboratorio pero surgen de diferentes causas. STEC-HUS se presenta con diarrea sanguinolenta; 60% de los pacientes desarrollan insuficiencia renal y requieren tratamiento de diálisis transitoria.

La *Escherichia Coli* es la principal causa, pero también se pueden hallar otras bacterias como Shigella dysenteriae. La PTT debe descartarse inicialmente dadas las implicaciones terapéuticas consistentes en tratar con plasmaféresis si TTP se confirma por el consumo de la actividad de ADAMTS 13. El SHU a está determinado

genéticamente y la vía Alterna del Complemento está implicada en la génesis de la enfermedad. Los microtrombos observados en la histología de la PTT tienen típicamente "coágulos blancos" compuestos por plaquetas. En el SHU hay "coágulos rojos" en los que predomina la fibrina y se puede observar un infiltrado inflamatorio. Histológicamente no hay diferencias entre SHU-STEC y aSHU, Las otras entidades que causan MAT deben ser consideradas a la hora de definir el manejo terapéutico a la luz de un posible enmascaramiento de un SHU a.

PALABRAS CLAVE: Síndrome hemolítico urémico atípico. Microangiopatía trombótica, diagnóstico. ADAMTS 13-13. Complemento. Toxina shiga. Trombocitopenia.

SUMMARY:

Atypical Hemolytic Uremic Syndrome (aHUS), Thrombotic Thrombocytopenic Purpura (TTP), Shiga Toxin Escherichia Coli Hemolytic Uremic Syndrome (STEC-HUS), Antiphospholipid Syndrome and other thrombotic microagiopathies (TMA), such as Progressive Systemic Sclerosis, Lupus Erythematosus, Human Immunodefinciency Virus, Preeclampsia, HELLP syndrome, drugs, Stem cell transplant have similar clinical forms of presentation and laboratory abnormalities but arise from different causes. STEC-HUS presents with bloody diarrhea, 60% of patients develop renal failure and require transient dialysis treatment.

Escherichia Coli is the major cause but other bacteria as Shigella dysenteriae could also be found. TTP should be ruled out since the beginning because of the possibility of prescribing plasmapheresis if TTP is confirmed by ADAMTS 13 activity consumption. aHUS is genetically determined, being the alternative complement pathway implicated in its pathophysiology. TTP microthrombi are typically "white clots" composed by platelets. Conversely, in HUS there are "red clots" since fibrin predominates and an inflammatory infiltrate can be seen. There are no other histological differences between STEC-HUS and aHUS. The other TMA causing entities should be considered due to al the possibility that they could mask an aHUS.

KEY WORDS: Atypical haemolytic uraemic syndrome. Thrombotic microangiopathy, diagnosis. ADAMTS 13-13. Complement. Shiga toxin. Thrombocytopenia.

DIFFERENTIAL DIAGNOSIS

Firstly, the Shiga toxin-producing *Escherichia coli* (STEC) hemolytic uremic syndrome (HUS) should always be ruled out, in a setting of thrombotic microangiopathy (TMA) and diarrhea, independently of the presence or not of blood in the stool[1]. Diarrhea, especially with blood, is a classic sign of enterohemorrhagic *Escherichia coli* enteritis/colitis in Shiga toxin-HUS[2]. Moreover, diarrhea is a well

established atypic hemolytic uremic syndrome (aHUS) trigger[3,4]. Besides, 30% of patients suffering from aHUS have diarrhea which can contain blood due to colonic infarctions[5-8]. The STEC- HUS is more frequently found in children, particularly in those younger than 2 years old[9,10]. Polymerase chain reaction (PCR) and culture of Shiga toxin-producing *Escherichia coli* should be used for diagnosing STEC-HUS since gastrointestinal signs are not enough for distinguishing STEC-HUS from aHUS[1].

Shiga toxin HUS or typical HUS (tHUS) presents with bloody diarrhea lasting typically 5 to 10 days, and 60% of patients develop renal failure and require dialysis for a period of ten days. Its mortality rate is about 4%, and *Escherichia coli* is the most common bacteria, although other bacteria (including Shigella dysenteriae) can also be found. Histologically there are no differences between tHUS and aHUS.

Therapeutic approach consists of supportive management (dialysis, antihypertensive drugs), but antibiotic are not recommended since they could kill beneficial bacteria allowing the Shiga toxin-producing Ecoli to proliferate. Regarding how to distinguish between HUS and thrombotic thrombocitopenic purpura (TTP), Adamts 13 activity can be used, since if ADAMTS 13 activity is abnormal (≤5%) TTP should be suspected. Conversely, a normal ADAMTS 13 activity (> 5%) is compatible with HUS[1].

When a thrombotic microangiopathy (TMA) with normal ADAMTS 13 activity, and absence of cobalamin C deficiency (diagnosed by high plasma homocysteine and methylmalonic acid levels) is found, a HUS can be suspected. However, there are reports of TTP not associated to severe ADAMTS 13 deficiency[10]. Besides, the number of platelets and serum creatinine values can help to distinguish between HUS and TTP, since platelets count is usually higher than 30,000 mm in aHUS, while TTP presents less than 20,000 mm[1]. Regarding serum creatinine, its levels are unusually greater than 2.3 mg/dl in TTP[1,11].

Thus, TTP classically involves the kidneys in more than 50% of cases, although with less severity than aHUS or tHUS. Additionally, the lungs are frequently involved in untreated aHUS but they are never directly involved in TTP[12-14].

The TTP should be ruled out since the beginning due to therapeutic strategy since plasmapheresis should be initiated if TTP diagnosis is confirmed by the ADAMTS 13 activity, and this test should be performed before plasma exchange therapy starts, but plasma exchange should be started before the result of the ADAMTS 13 test. Besides, neurological and renal abnormalities are often presents.

RENAL BIOPSY (RB)

TMA can be diagnosed by RB in the absence of peripheral blood schistocytes or significant major peripheral TMA expression. RB can present subendothelial edema in arterioles and glomerular capillary loops, associated or not with luminal fibrin microthrombi[15]. Even though, HUS is usually clinically diagnosed, RB can be useful for confirming TMA diagnosis, by showing microthrombi and vessels occlusions, when is difficult its clinical diagnose[1,16]. The TTP microthrombi have typically

"white clots" composed by platelets and von Willebrand factors, with few amounts of fibrin, and minimal or absence of vascular or perivascular infiltration of inflammatory cells[16-19]. Conversely, in HUS there are "red clots" in which fibrin predominates and an inflammatory infiltrate can be seen[17,18]. A HUS cannot be distinguished from STEC - HUS based on the renal pathology. The C5B-9 deposits on microvessels can be seen in HUS RB. Glomerular mesangiolysis and membranoproliferative glomerulonephritis are acute and chronic TMA findings, respectively. Electron microscopy usually shows endothelial cell swelling, necrosis, and distinction between platelet and fibrin microthrombi[19].

RESPONSE TO PLASMAPHERESIS (PF)

A complete response to PF is defined by normalization of hemoglobin, LDH, and platelet count and a decrease of at least 25% of serum creatinine from their baseline value, after PF has been completed[1]. However, PF response can also be defined in terms of the number of PF required. Eighty per cent of aHUS patients can also have dramatic response to PF based on platelet count, hemoglobin, and haptoglobin normalization, and LDH decline [18-20].

In TTP, platelet count normalization after PF is a result of platelet function normalization with little expression of activation markers such as P-selectin (assessed by flow citometry). Conversely, in aHUS platelet count normalization after PF is also a consequence of their functional improvement, but platelet activation persists with high expression of P-selectin[19]. Most of aHUS patients treated only with plasmapheresis can have a complete or almost complete hematologic remission[21].

Zuber et al. has suggested that when platelet count and serum creatinine level do not ´improve after five PF sessions, it should be suspected the diagnosis of aHUS instead of TTP.

Sometimes, glucocorticoids are prescribed together with the plasma exchange when TTP diagnoses is suspected but the result of ADAMTS 13 activity test is delayed, in order to also treat alternative etiologic conditions such as the Idiopathic Thrombocytopenic Purpura (ITP); besides they are also useful in those cases where there is no an increase in the platelet count after the plamapheresis exchange therapy. Nonetheless use of glucocorticoids is not recommended in any kind of HUS treatment.

TMA: DIFFERENTIAL DIAGNOSIS

There is a variety of physiologic or pathologic conditions which activate the complement system, and represent differential diagnosis of TMA. Among these conditions are pregnancy, HELLP syndrome, infection, autoimmune disease (systemic erythematosus lupus and scleroderma), malignant hypertension, tissue and organ transplant, and some drugs. Last HUS Consensus classified these conditions as secondary HUS and shows that there is a small difference between them and aHUS. Thus, if TMA signs and symptoms do not solve after the complement- activating condition has been treated or HUS inducing medication has been discontinued, it could be an unmasked aHUS or TTP[15]. It is worth mentioning some characteristics

regarding the main causes of secondary HUS[21-27]:

Pregnancy:

TMA secondary to pregnancy which solves after delivery is almost always HELLP or Preeclamsia, while TMA which occurs late in the third trimester or post-partum is usually aHUS[23]. When a TTP persists after delivery, it can continue presenting low platelet count but improves renal function; conversely, aHUS normalizes platelets count and worsens renal function after pregnancy.Thus , TMA s of HELLP syndrome that occurs late in pregnancy and do not solve after pregnancy should be considered possibly as masked aHUS.

Systemic Lupus Erythematosus (SLE):

Nephritis exacerbation in previously diagnosed SLE can be interpreted as aHUS if capillary thrombi are proved in RB and it is refractory to usual treatment.

Malignant Hypertension:

If renal function does not improve in patients who had renal injury after hypertension crisis after blood pressure is already controlled, TMA diagnosis should be suspected. In this context, persistence of anemia, thrombocytopenia, and renal injury could be interpreted as aHUS.

Bone marrow transplant:

Persisting TMA despite graft vs. host disease resolution, mTOR or calcineurin inhibitor discontinuation or infection resolution might raise the suspicion of a different process with commitment of the alternate complement that is not self-limiting with the usual measures.

Medication:

It is supposed that discontinuation of MTA inducing drugs (eg: calcineurin or rapamycin) makes this entity to disappear after one half- life (3-4 and 7-8 days, respectively). Thus, if after MAT inducing drugs discontinuation this entity does not resolve, aHUS should be suspected.

TMA related to the antiplatelet agent ticlopidine and possibly also to clopidogrel may unmask aHUS in a genetically susceptible individual even if ADAMTS 13 activity and inhibitor level are suggestive of TTP.

Renal transplantation:

The incidence of TMA in renal transplant patients has been reported to be 4.9 episodes per 1000 person-years at-risk. It may be associated to transplant itself, anti-calcineurin, mTOR inhibitor, humoral rejection, or cytomegalovirus infection.

Complement system mutations have also been found in 27% of patients with post-transplant HUS associated to calcineurin inhibitors, as well as in 33% of patients with HUS associated to autoimmune diseases. Additionally, TMA documented in patients on some chemotherapeutic agents, vascular endothelial growth factor (VEFG) inhibitors, anti graft vs. host disease (anti -GVHD) medication or extended-release opiates, which does not solve after these agents withdrawal, could be consider aHUS.

Other conditions:

When thrombin is generated in an acute coagulation disorder, there is a positive feedback between thrombin generation, C5 cleavage, since thrombin functions as a C5 convertase, and participates in C5a and C5b-9 formation. In an individual genetically susceptible to aHUS, TTP could unmask aHUS[30]. 60% of aHUS cases are associated with an identifiable complement activating condition. These conditions include autoimmune diseases, infections, malignant hypertension, pregnancy, organ and tissue transplant and treatment with chemotherapeutic or anti GVHD medication. In order to distinguish aHUS unmasked by those conditions from secondary TMA, it should be treat these complement activating conditions and assess whether TMA has resolved.

Diseases such as postpartum HUS has now been considered aHUS in 86% of cases (positive genetic test). Other entities when presented with TMA, such as malignant hypertension, post-transplant HUS associated to calcineurin inhibitors (27%), patients with HUS associated to autoimmune diseases (33%) were found to have mutations in the complement system. It should to be alert in these cases mainly when they are refractory to the usual treatment.

ECULIZUMAB in aHUS

Eculizumab is a recombinant humanized monoclonal anti-C5 antibody, which inhibits complement factor 5a (C5a) and subsequent formation of the membrane-attack complex (MAC). It was initially licensed for paroxysmal nocturnal hemoglobinuria treatment, and recently approved to treat aHUS[28-30] In 2011, Weitz et al. reported the first successful kidney transplantation in a child suffering from aHUS after the prophylactic administration of eculizumab[31].

In 2012, Zuber et al. reported nine patients who received prophylactic eculizumab therapy to prevent post-transplant aHUS recurrence, eight of whom experienced a successful recurrence-free post-transplant course, while one lost his graft due to early graft artery thrombosis. Overall, these data suggest that long-term eculizumab treatment is highly effective to prevention post-transplant aHUS recurrence. However, it has not established yet guidelines indicating the eculizumab dose to prevent aHUS.

Legendre et al. have recently published the results of two trials that studied the efficacy of eculizumab in adults and adolescents with aHUS resistant to plasma therapy. These two trials together included 15 kidney transplant recipients. In both trials, the primary end point (normalization of platelet count and TMA-free status, respectively) was achieved in 80% of the patients. Eculizumab initiation was clearly associated with the recovery of renal function in both transplanted and non-

transplanted patients[34]. Terminal complement blockade with eculizumab was directly correlated with sustained, long-term (>2.5 years) marked improvements in renal but also cardiac function in pediatric patients suffering from atypical hemolytic uremic syndrome[33].

In adult patients with suspected aHUS, early initiation of eculizumab is recommended. Eculizumab treatment should be considered in cases where complete hematologic recovery and renal function are not observed after initiation of plasmapheresis and plasma exchange. In this sense, the French Study Group of SHUa recommends transferring the patient to eculizumab when, after the fifth plasmapheresis session, normalization of platelets or LDH levels or a reduction of plasma creatinine $\geq$ 25% cannot be achieved.

When SHUa diagnosis is unequivocal, the treatment of choice is eculizumab. The precocity in its administration guarantees the reversibility of the hematological picture and avoids renal injury. Prior to the administration of eculizumab, it is necessary to vaccinate all patients against Neisseria meningitidis (preferably tetravalent vaccines conjugated to serotypes A, C, Y and W135, and serotype B). If the administration of eculizumab cannot be delayed until the response to vaccination is obtained, this treatment should be associated with antibiotic coverage against Neisseria meningitidis and antibiotic prophylaxis may be initiated according to the hospital protocol with penicillin or amoxicillin.

In adult patients it is recommended to maintain antibiotic prophylaxis while administering eculizumab according to medical criteria and individualized assessment of the patient. New considerations are being taken into account today in relation to the diagnosis of aHUS.

This ultra rare genetic disease considered in the past as being centainly familial, of appearance at childhood and affecting both male and female has been transformed into a disease diagnosed in adulthood,with a high frequency seen in women suffering from post - partum TMA, mainly associated to renal transplant TMA refractory to usual assessment and treatment, and in the majority of cases without family relationships.

CONCLUSION:

The differentiation of typical and atypical HUS versus TTP is based mainly on the recognition of TMA, the measurement of ADAMTS 13 activity, number of platelets and serum creatinine values which help to distinguish between HUS and TTP, since platelets count is generally greater than 30,000 mm in aHUS, while TTP usually presents with less than 20,000 mm. Regarding serum creatinine, its levels are unusual over 2.3 mg/dl in TTP.

Thus, TTP classically involves the kidneys in more than 50% of cases, although with lower severity than in aHUS or tHUS. The lungs are frequently involved in untreated HUS but they are never directly involved in TTP. Since the beginning, it is necessary to rule out STEC-HUS.

The manifestations of TMA which is considered as "secondary" in various entities with refractoriness to treatment should exclude superimposed aHUS.

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It is worth mentioning that among the secondary thrombotic microangiopathies is the POEMS syndrome' nephropathy, which is a associated to humoral factors such as the vascular endothelial growth factor (VEGF), and the treatment of this condition induces serum VEGF reduction, and glomerular filtration rate recovery.

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Comment of the reviewer Susana Gabriela Pérez MD. Especialista en Nefrología. Posgrado de Efectividad Clínica, Analista de Datos Médicos en Diaverum. Argentina.

Hemolytic uremic syndrome is a thrombotic microangiopathy characterized by intravascular hemolysis, thrombocytopenia, and acute renal failure. This syndrome is classified as a typical form, caused by infection with Shiga toxin-producing *Escherichia coli*, or as an atypical form that is mainly associated with mutations or autoantibodies that lead to deregulated complement activation. In some patients, a secondary form with a disease or trigger such as autoimmunity, transplantation, cancer, infection, certain cytotoxic drugs, or pregnancy occurs.

In all cases, the consequence is simultaneous damage to endothelial cells, the production of intravascular hemolysis and the activation of platelets leading to a procoagulative state, with formation of microthrombi and tissue damage.

The vicious circle of complement activation, damage to endothelial cells, platelet activation and thrombosis, can be stopped by the inhibition of therapeutic complement in the majority of patients with typical, atypical and some secondary forms.

Therefore, understanding the pathogenesis of different forms of HUS may be useful in clinical practice.

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