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GENERAL INFORMATION

Atypical uraemic haemolytic syndrome in pregnancy☆

Ángel Augusto Pérez-Calatayud[a,*], Jesús Carlos Briones-Garduño[a], Mercedes del Pilar Álvarez-Goris[a], Ricardo Sánchez Zamora[a], Angélica A. Torres Aguilar[a], Rosa Elba Mendoza-Morales[b]

[a] *Medicina Crítica en Obstetricia, Hospital General de México Dr. Eduardo Liceaga, Ciudad de México, Mexico*
[b] *Instituto Ingenes, Ciudad de México, Mexico*

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KEYWORDS
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Abstract Atypical haemolytic uraemic syndrome is one of the main variants of thrombotic microangiopathy, and is characterised by excessive complement activation in the microvasculature. It is also characterised by the clinical triad; non-immune haemolytic anaemia, thrombocytopenia, and acute renal failure. In addition, 60% of patients have mutations in the genes encoding complement regulators (factor H, factor I, membrane cofactor proteins, and thrombomodulin), activators (factor B and C3), as well as autoantibodies against factor H. Multiple factors are required for the disease to manifest itself, including a trigger and gene mutations with adequate penetration. Being one of the differential diagnoses of preeclampsia–eclampsia and HELLP syndrome means that the clinician must be familiar with the disease due to its high mortality, which can be modified with early diagnosis and comprehensive treatment.

PALABRAS CLAVE
Síndrome urémico hemolítico atípico;
Microangiopatía trombótica;
Embarazo

Síndrome urémico hemolítico atípico en el embarazo

Resumen El síndrome hemolítico urémico atípico es una variante de la microangiopatía trombótica, caracterizado por una excesiva activación del complemento. Se caracteriza por presentar anaemia hemolítica no autoinmune, trombocitopenia y falla renal aguda. Se ha observado que el 60% de los pacientes presentan mutaciones en los genes que codifican al complemento, tanto reguladores (factor H, factor I, cofactor de proteínas de membrana y trombomodulina),

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* Corresponding author at: Unidad de Terapia Intensiva, Ginecología y Obstetricia, Hospital General de México Dr. Eduardo Liceaga, Eje 2A Sur (Dr. Balmis) 148, Col.: Doctores. C.P. 06726, Deleg.: Cuauhtémoc, Ciudad de México, Mexico. Tel.: +52 55 44584640 ext. 1612.
E-mail address: gmemiinv@gmail.com (Á.A. Pérez-Calatayud).

activadores (factor B y C3) como autoanticuerpos contra el factor H. Se requiere la presencia de múltiples factores para su manifestación, estos incluyen: un disparador y mutaciones de genes con la penetrancia adecuada. Es necesario que el clínico esté familiarizado con la enfermedad, ya que presenta una elevada morbimortalidad que puede ser modificada si se identifica de manera temprana y se da un tratamiento oportuno.

Background

Atypical haemolytic uraemic syndrome is a variant of the thrombotic microangiopathy which is characterised by the following clinical triad: non-autoimmune haemolytic anaemia, thrombocytopenia and acute kidney failure.[1,2]

It is characterised by an irregularity of the complement system, caused by genetic mutation of its inhibitors.[2] Malignant hypertension, septicaemia, auto-immune disorder (lupus, scleroderma), streptococcal infections, pregnancy, HELLP syndrome and cancer may be the cause of this syndrome.[3]

Traditionally, haemolytic uraemic syndrome is classified in 2 ways: typical haemolytic uraemic syndrome which peaks in incidence in children and is caused by enteric infections secondary to bacteria which are producers of the Shiga toxin (Fig. 1) and atypical haemolytic uraemic syndrome which in 50–60% of cases is associated with patients with gene mutations within the complement system, which in the majority of patients leads to terminal chronic kidney failure and the need for a kidney transplant.[4–6]

Pregnancy may be a trigger of this disease, particularly during the postnatal period. This is the result of the complement system playing a significant role in the physiopathology of pregnancy. It increases to prevent the damage caused by the placenta through the trophoblastic expression of complement regulatory proteins, known as the aggravating factor in degradation, the membrane cofactor protein (MCP) and CD59.[5–7]

There is a reduction of these proteins in the postnatal period, or a reduction in the majority complement proteins, which lead to the appearance of disease.[7]

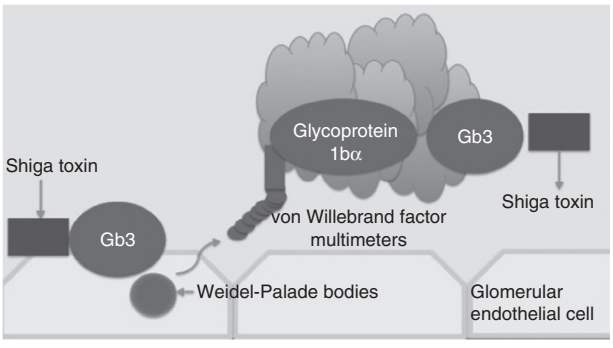

Figure 1 Haemolytic uraemic syndrome secondary to enteric infection caused by the Shiga toxin.

Epidemiology

Thrombotic microangiopathy associated with pregnancy (P-TMA) has an incidence of 1 case in every 250,000 pregnancies.[8–10] There are reports of an incidence of atypical haemolytic uraemic syndrome of 2 cases for every 1,000,000 inhabitants.[11] In women of reproductive age the phenotype of atypical haemolytic uraemic syndrome presents in late pregnancy or in the immediate postpartum period.[11] In 10% of patients with this syndrome, the onset of pregnancy is the trigger.[12]

Physiopathology

The complement system is one of the main mechanisms involved in immunity measured by antibodies, and is considered to be a bridge between innate and adaptive immunity, which offers: protection against bacterial infection, enhancement of the elimination of immune complexes and inflammatory products, protection against external agents and the regulation of cellular apoptosis.[13] There are 3 independent pathways for its activation: classical, lectin and alternative.[14] Activation needs to be regulated to prevent tissue damage, particularly when activated by the alternative pathway.[15] In the majority of patients affected by atypical haemolytic uraemic syndrome its development is related to uncontrolled activation of the complement pathway and with a growing number of genetic mutations which have already been identified for the activation of this syndrome.[15] These mutations are observed in the genes which regulate the function of the complement, such as complement H (FCH) factor inhibitors. Richard[16] identified the importance of the mutations of this gene as a cause of haemolytic uraemic syndrome. He discovered mutations of the FCH gene in exons 18–20 of 2 familial and 3 sporadic patients out of the 19 familial and 31 sporadic patients studied.[15] Furthermore, this study showed that the familial haemolytic uraemic syndrome is a heterogeneous condition. Rodríguez[17] discovered that the mutations in the FCH regulators, the complement I (FCH) factor and PCM led to the loss of the complement functioning, whilst those of C3 activated functioning (Fig. 2). PCM (CD46) is a transmembrane regulatory complement which is broadly expressed as FCH, and Richards[18] discovered a PCM (CD46) mutation in individuals of 3 familials, who presented a deletion of 2 amino acids (D237/S238) in the familial 1 (heterozygote) and a