A retrospective study of pregnancy-associated atypical hemolytic uremic syndrome

Ana Huerta[1,2], Emilia Arjona[3,4], Jose Portoles[1,2], Paula Lopez-Sanchez[1], Cristina Rabasco[2,5], Mario Espinosa[2,5], Teresa Cavero[2,6], Miquel Blasco[2,7], Mercedes Cao[8], Joaquin Manrique[9], Virginia Cabello-Chavez[10], Marta Suñer[10], Manuel Heras[11], Xavier Fulladosa[2,12], Lara Belmar[2,13], Amparo Sempere[14], Carmen Peralta[15], Lorena Castillo[15], Alvaro Arnau[16], Manuel Praga[2,6] and Santiago Rodriguez de Cordoba[3,4]

[1]Department of Nephrology, Hospital Universitario Puerta de Hierro Majadahonda, Madrid, Spain; [2]RedinRen RD016/009/009, Instituto de Salud Carlos III, Madrid, Spain; [3]Department of Cellular and Molecular Medicine, Center for Biological Research, Madrid, Spain; [4]Center for Biomedical Network Research on Rare Diseases, Madrid, Spain; [5]Department of Nephrology, Hospital Universitario Reina Sofía, Córdoba, Spain; [6]Department of Nephrology, Hospital 12 de Octubre, Madrid, Spain; [7]Department of Nephrology, Hospital Clínic de Barcelona, Barcelona, Spain; [8]Department of Nephrology, Complexo Hospitalario Universitario A Coruña, A Coruña, Spain; [9]Department of Nephrology, Clinica Universitaria de Navarra, Pamplona, Spain; [10]Department of Nephrology, Hospital Universitario Virgen del Rocío, Seville, Spain; [11]Department of Nephrology, Complejo Asistencial de Segovia, Segovia, Spain; [12]Department of Nephrology, Hospital de Bellvitge, Barcelona, Spain; [13]Department of Nephrology, Hospital Universitario Marques de Valdecilla, Santander, Spain; [14]Department of Hematology, Hospital Universitari Politecnic La Fe, Valencia, Spain; [15]Department of Nephrology, Hospital Universitari de Tarragona Joan XXIII, Tarragona, Spain; and [16]Department of Nephrology, Hospital Universitario Donostia, Donostia, Spain

Pregnancy-associated atypical hemolytic uremic syndrome (aHUS) refers to the thrombotic microangiopathy resulting from uncontrolled complement activation during pregnancy or the postpartum period. Pregnancy-associated aHUS is a devastating disease for which there is a limited clinical understanding and treatment experience. Here we report a retrospective study to analyze the clinical and prognostic data of 22 cases of pregnancy-associated aHUS from the Spanish aHUS Registry under different treatments. Sixteen patients presented during the first pregnancy and as many as nine patients required hemodialysis at diagnosis. Identification of inherited complement abnormalities explained nine of the 22 cases, with *CFH* mutations and *CFH* to *CFHR1* gene conversion events being the most prevalent genetic alterations associated with this disorder (66%). In thirteen of the cases, pregnancy complications were sufficient to trigger a thrombotic microangiopathy in the absence of genetic or acquired complement alterations. The postpartum period was the time with highest risk to develop the disease and the group shows an association of cesarean section with pregnancy-associated aHUS. Seventeen patients underwent plasma treatments with a positive renal response in only three cases. In contrast, ten patients received eculizumab with an excellent renal response in all, independent of carrying or not inherited complement abnormalities. Although the cohort is relatively small, the data suggest that pregnancy-associated aHUS is not different from other types of aHUS and suggest the efficacy of eculizumab treatment over plasma therapies. This study may be useful to improve prognosis in this group of aHUS patients.

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Correspondence: *Ana Huerta, Hospital Universitario Puerta del Hierro Majadahonda, Department of Nephrology, Majadahonda, Madrid 28222, Spain. E-mail: ana.huerta@me.com, or Santiago Rodriguez de Cordoba, Department of Cellular and Molecular Medicine and Center for Biological Research and Center for Biomedical Network Research on Rare Diseases, Spain. E-mail: srdecordoba@cib.csic.es*

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Atypical hemolytic uremic syndrome (aHUS) is a thrombotic microangiopathy (TMA) associated with genetic or acquired abnormalities that result in uncontrolled complement activation, leading to kidney failure and other extrarenal complications.[1] The term pregnancy-associated aHUS (P-aHUS) has been coined to refer to the TMA that result from uncontrolled complement activation during pregnancy or the postpartum period. P-aHUS is a devastating systemic disease, with high maternal mortality and morbidity rates that extends beyond the initial presentation. It is a rare condition with an incidence of 1 in every 25,000 pregnancies and accounts for 20% of all aHUS cases in women.[1–3]

During the last decade there has been enormous progress in the clinical and pathophysiological understanding of aHUS, which have greatly improved the management and treatment of the aHUS patients. The implementation of a complement inhibition therapy, based on the use of eculizumab, has changed the natural history of the disease,

preventing in most of the patients the adverse consequences of the complement dysregulation. Characterization of the etiological factors predisposing the patient to aHUS and identification of the concurrent triggering events that result in the development of aHUS have nowadays become essential for an individualized management of the aHUS patients, including long-term treatment with eculizumab.[4–10]

Despite these advances, specific clinical data in P-aHUS, incidence of genetic predisposing factors and knowledge of the nature of complement activating triggers that may occur during pregnancy or the postpartum period are still scarce and mostly limited to the original work published by Fakhouri *et al.*[2] in 2010. In their report, the French group reported the first series of P-aHUS patients, providing novel and valuable information of this form of aHUS. Particularly relevant was their finding that up to 86% of their patients presented a complement genetic abnormality. In their series the postpartum was reported as the main period of onset of the disease and the second pregnancy that of highest risk for P-aHUS development. The prognosis in that cohort was very poor, especially from a renal point of view, with up to 62% of the patients reaching end-stage renal disease (ESRD) within the first month after aHUS onset. However, it must be emphasized that the study was performed in the pre-eculizumab era. Subsequently, only a small number of case reports and very small series have reported the efficacy of eculizumab in P-aHUS patients.

Here we describe a Spanish cohort of P-aHUS including 22 patients to provide epidemiologic, clinical, and prognostic data of the disease. We also report the incidence of complement abnormalities in the aHUS candidate genes and discuss their role in aHUS pathogenesis. Most importantly, we report our experience with the use of plasma treatment and eculizumab in a significant number of patients within our P-aHUS cohort. These data, together with that generated from other P-aHUS cohorts should provide clues to anticipate situations of aHUS risk during pregnancy and to treat efficiently P-aHUS when it develops.

RESULTS

Demographics and clinical data

A search in our Spanish aHUS database for adult women with P-aHUS (n = 242) resulted in the identification of 22 patients (9%). These patients were referred to us for genetics and molecular complement analysis from 13 different Spanish hospitals. Relevant clinical and biological data from most of these patients (n = 22) was collected by examining their medical records (Table 1). All patients were born in Spain and none presented with an autoimmune-associated disease. Median age was 33.9 years (interquartile range [IQR]: 25, 38.3). At the time of the event none of the patients had a familial history of aHUS. In 4 patients (18%), the P-aHUS was a recurrence of a previously diagnosed aHUS. One patient had chronic kidney disease of diabetic etiology and carried a combined pancreas-kidney transplant with normal functioning kidney (serum creatinine: 0.8 mg/dl) at the onset of the P-aHUS event. Notably, in 16 patients the P-aHUS occurred during the first pregnancy (73%) and, interestingly, among the 6 patients with previous pregnancies, 4 of those pregnancies ended in a successful vaginal birth without any complications and in 2 resulted in abortions.

The P-aHUS onset

In 6 patients (27%), the event occurred during the antepartum period, and in 16 patients (73%), it occurred in the postpartum period, mostly within the first week after delivery (Figure 1). Importantly, 13 patients within the postpartum group (81%) delivered their babies by cesarean section (C-section), and 3 of them were associated with severe bleeding. Seven of these patients underwent C-section for reasons related to the mechanics of delivery (e.g., podalic presentation of the fetus, cephalopelvic disproportion, failure to induce delivery). Notably, C-section was due to a suspected preeclampsia in only 3 patients. In another patient, the cause was because of vaginal hemorrhage, but interestingly, the aHUS episode in this patient occurred 4 weeks after delivery. Finally, the reason for the C-section in 2 patients was not reported.

Six women had the P-aHUS episode before delivery. Three developed P-aHUS at week 36 and delivered healthy babies. One had a vaginal delivery at week 32 of an underweight (1500 g) but healthy child. Another P-aHUS case had the onset at week 19, but the pregnancy was maintained with eculizumab during 5 more weeks. She delivered a baby with very low weight (500 g) by C-section, who was hospitalized for 5 months and is today a healthy child. Finally, there was 1 case of therapeutic abortion at week 19 due to "hydrops fetalis." Based on the information included in the medical records, alternative aHUS triggers, such as infections or drugs were excluded in all cases of P-aHUS included in this report.

Nineteen patients presented with hypertension (86%). Extrarenal manifestations were also present in several patients: 7 patients had neurological complications, 4 had gastrointestinal alterations, and 3 had cardiac affectation, without peripheral vasculopathy.

Nine patients (41%) required acute hemodialysis. Maximum serum creatinine among patients who did not required acute hemodialysis was 3.5 mg/dl (IQR: 2.3, 4.23), minimum hemoglobin level was 6.9 g/dl (IQR: 5.3, 7.8), minimum platelets count was 50×10^9/l (IQR: 30×10^9, 65×10^9), maximum levels of lactic acid dehydrogenase were 1977 UI/l (IQR: 879, 3338) and maximum proteinuria reached 2.5 g/d (IQR: 1.6, 4.8). All patients presented schistocytes in the blood smear and decreased haptoglobin. Microhematuria could not be assessed because of the presence of lochia. Renal biopsies were available for 11 patients and histologic lesions characteristic of thrombotic microangiopathy were described with 1 exception. An associated glomerulonephritis (GN) was also described in 3 cases (2 C3GN and 1 immune complex-mediated membranoproliferative GN). A fourth patient, who later receive a transplant, developed a *de novo* C3GN in the graft.