Pregnancy-associated atypical hemolytic uremic syndrome; a retrospective study from the Spanish Registry.

Ana Huerta^{1,2*}, Emilia Arjona³, Jose Portoles^{1,2}, Paula Lopez-Sanchez¹, Cristina Rabasco^{4,2}, Mario Espinosa^{4,2}, Teresa Caverio^{5,2}, Miquel Blasco^{6,2}, Mercedes Cao⁷, Joaquin Manrique⁸, Virginia Cabello-Chavez⁹, Marta Suñer⁹, Manuel Heras¹⁰, Xavier Fulladosa^{11,2}, Lara Belmar^{12,2}, Amparo Sempere¹³, Carmen Peralta¹⁴, Lorena Castillo¹⁴, Alvaro Arnau¹⁵, Manuel Praga^{5,2} and Santiago Rodriguez de Cordoba^{3*}

1. Department of Nephrology, Hospital Universitario Puerta de HierroMajadahonda, Madrid, Spain.
- 2.RedinRen RD 016/009/009 ISCIII, Spain.
3. Department of Cellular and Molecular Medicine and Center for Biological Research and Center for Biomedical Network Research on Rare Diseases. Spain.
4. Department of Nephrology, Hospital Universitario Reina Sofía, Córdoba, Spain.
5. Department of Nephrology, Hospital 12 de Octubre, Madrid, Spain.
- 6.Department of Nephrology, Hospital Clínic de Barcelona, Spain.
7. Department of Nephrology, ComplejoHospitalarioUniversitario A Coruña, Spain.
8. Department of Nephrology, ClinicaUniversitaria de Navarra, Pamplona, Spain.
9. Department of Nephrology, Hospital. Universitario Virgen delRocío, Seville, Spain.
10. Department of Nephrology, Complejo Asistencial de Segovia, Segovia, Spain.
11. Department of Nephrology, Hospital de Bellvitge, Barcelona, Spain.
12. Department of Nephrology, Hospital Universitario Marques de Valdecilla, Santander, Spain.
13. Department of Hematology, Hospital Universitari Politecnic La Fe, Valencia, Spain.
14. Department of Nephrology, Hospital Universitari de Tarragona Joan XXIII, Tarragona, Spain.
15. Department of Nephrology, Hospital Universitario Donostia, Spain.

(*) Equalcorrespondenceauthors: Ana Huerta (ana.huerta@me.com) and Santiago Rodriguez de Cordoba (srdecordoba@cib.csic.es)

Running Title: P-aHUS, a retrospective study from the Spanish Registry.

Keywords: Postpartum, hemolytic uremic syndrome, eculizumab, complement,

caesarean section.

SUMMARY

Pregnancy-associated atypical hemolytic uremic syndrome (P-aHUS) refers to the thrombotic microangiopathy that result from uncontrolled complement activation during pregnancy or the postpartum period. P-aHUS is a devastating disease for which we still have a limited clinical understanding and treatment experience. Here we report a retrospective study to analyze the clinical and prognostic data under different treatments of 22 cases of P-aHUS from the Spanish aHUS Registry. Most patients presented during the first pregnancy (73%) and as many as 41% required hemodialysis at diagnosis. The identification of inherited complement abnormalities explains 41% of cases (9/22), with *CFH* mutations and *CFH* to *CFHR1* gene conversion events being the most prevalent genetic alterations associated with P-aHUS (66%). The data suggest that in 59% of our P-aHUS cases the pregnancy complications are sufficient to trigger a thrombotic microangiopathy in the absence of genetic or acquired complement alterations. We confirm the postpartum period is the time with highest risk to develop the disease and show an association of caesarean section with P-aHUS in our cohort. 17 patients (77%) underwent plasma treatments with a positive renal response in only 3 of cases (18%). In contrast, 10 patients in our cohort (45%) received eculizumab with an excellent renal response in all of them, independently of carrying or not inherited complement abnormalities. Our cohort is relatively small, but the data indicate that P-aHUS is not different from other types of aHUS and suggest the efficacy of eculizumab treatment over plasma therapies. These data should be useful to improve prognosis in this group of aHUS patients.

INTRODUCTION

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 extra renal 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 an 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.* in 2010.² 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 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 epidemiological, 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 important, 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 (25-38.3 IQR). At the time of the event none of the patients had a familial history of aHUS. In four 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 (sCr 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 and in 16 patients (73%) 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 caesarean section (C-section), three of them associated with severe bleeding. Seven of these patients underwent C-section for reasons related to the mechanics of delivery (podalic presentation of the fetus, cephalopelvic disproportion, failure to induce delivery, etc). 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 four weeks after delivery.

Finally, the reason for the C-section in two 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 (1500g) but healthy child. Another P-aHUS case had the onset at week 19, but was maintained with eculizumab during 5 more weeks. She delivered a baby with very low weight (500g) by C-section, who was hospitalized for 5 months and is today a healthy child. Finally, there was one case of therapeutic abortion at week 19 due to “hydrops fetalis”. Based on the information included in the medical records, alternative aHUS triggers, like infections or drugs were excluded in all cases of P-aHUS included in this report.

Nineteen patients presented with hypertension (86%). Extra renal 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 (2.3-4.23 IQR), minimum hemoglobin level was 6.9 g/dL (5.3-7.8 IQR), minimum platelets count was $50 \times 10^9/L$ ($30-65 \times 10^9$ IQR), maximum levels of LDH were 1977 UI/L (879- 3338 IQR) and maximum proteinuria reached 2.5 g/day (1.6-4.8 IQR). All patients presented schistocytes in the blood smear and decreased haptoglobin. Microhematuria could not be assessed because of the presence of loquios. Renal biopsies were available for 11 patients and histological lesions characteristic of thrombotic microangiopathy were described with one exception. An associated glomerulonephritis was also described in 3 cases (2 C3 glomerulonephritis (C3GN) and 1 immune complex-mediated membranoproliferative GN). A fourth patient, who was later on transplanted, developed a “de novo” C3G in the graft.

Genetics and molecular analysis of complement analysis in patients with P-aHUS

Complement analysis and genetic findings in the 22 patients are depicted in Table 2 and described in Supplementary Methods. Four patients presented decreased levels of C3. A complement abnormality in the aHUS candidate genes was detected in 9 of 22 patients (41%), which is significantly less than the 86% reported previously.² Three patients (14%) carried a mutated *CFHR1* gene, another three (14%) had a *CFH* mutation, two had a *C3* mutation (9%) and one (4%) had a *CFI* mutation. A total of 13 patients (59%) had no detected genetic defect.

All genetic variants detected in the patients were confirmed to be pathogenic. The product of the mutated *CFHR1* gene encodes a mutant FHR-1 protein with the C-terminal region identical to that of FH. This abnormal FHR-1 protein competes the binding of FH to the cell surfaces and impairs complement regulation. Two of the *CFH* mutations introduce stop codons in the *CFH* sequence that results in FH deficiencies and the third one is a missense mutation in the N-terminal of FH that impairs the cofactor and decay accelerating activities of FH. Finally, the *CFI* mutation is a missense mutation that impairs expression and associates with decreased levels of FI in plasma^{11,12} and the two *C3* mutations are known *C3* pathogenic variants that have been previously described associated with aHUS and that impair binding to C3b of the complement regulators.¹³⁻¹⁵

The genotypes for the at-risk *MCP*_{GGAAC} and *CFH-H3* haplotypes were also determined in all patients. The allele frequencies of both at-risk haplotypes were significantly elevated compared with the allele frequencies in the normal Spanish population (*MCP*_{GGAAC}, 0.43 vs 0.23; *CFH-H3*, 0.45 vs 0.20). Notably, 7 of the 22 patients were homozygous for the at-risk *MCP*_{GGAAC} haplotype, which exceeds slightly the expected number from the 0.43 allele frequency. Two patients presented the *CFHR3-CFHR1* deletion in homozygosis, but anti FH auto antibodies were not detected.

Interestingly, the percentage of adult aHUS patients in the whole Spanish aHUS cohort carrying complement gene alterations (39%; n=280) is very similar to that observed in the P-aHUS cohort (41%). This is, however, much higher than the percentage of patients carrying genetic alterations among those reported by the referral physicians as secondary TMA, excluding P-aHUS (11%, n= 57). Notably, no mutations in *MCP* or anti-FH antibodies were detected in any of the patients and none of the patients carried more than one mutation.

Treatment and evolution

Ten patients (45%) received eculizumab at the P-aHUS event and all of them (100%) had a positive response at both hematological and renal levels. Eculizumab was initiated with a median time of 17 days (8-23 IQR) after the P-aHUS event and treatment lasted 9.8 months (7.4-12.3 IQR) on average, estimated by Kaplan Meier. In 9 of the 10 cases, eculizumab was initiated because of the lack of response to plasma therapies. The remaining case was a woman with a previous diagnosis of aHUS who had a relapse during pregnancy. No severe adverse effects were observed in the eculizumab treated patients that forced treatment discontinuation.

Seventeen patients were treated with plasmapheresis (77%), with an average of 6 sessions per patient (5-12 IQR). Plasma treatments were initiated with a median time of 2 days (1-3 IQR) after the P-aHUS event (estimated by Kaplan Meier). All but 2 patients underwent daily treatment during the first week and then every 48hours. Two patients were treated every 48 hours from the beginning. Treatment lasted a median time of 7.5 days (4-15 IQR). In eight patients there was a hematological response (47%), but only three had a renal response (18%). Three patients received fresh frozen plasma (1-64 infusions). All of them had a good hematological response and two had a renal response (67%). Additionally, two patients were treated with corticosteroids without response and one evolved favorably after heparin treatment. Follow up time

was on average 7.9 years/patient (accumulated time 173.2 years).

One patient died 28 years after the P-aHUS episode at 65 years old. 4 of the 22 patients ended in ESRD (18%) within the first month after the P-aHUS event and at the end of the follow-up 6 of the 22 patients (27%) required RRT. All these patients have received a renal transplant during the follow up. Three of them (50%) lost their grafts due to recurrence of the disease (one patient lost two grafts); two were carriers of pathogenic variants in complement components. A fourth patient, with no detected mutation, lost her first graft due to a “*de novo*” C3G and in her second transplant had an aHUS episode that was resolved with eculizumab (Table 1).

Seven patients had aHUS recurrences. The time to have a relapse was on average 240 months (134.2-346.6 IQR), estimated by Kaplan Meier. Four of them were carriers of pathogenic complement variants, but the other three had no detected genetic or acquired defect. In four of the seven patients the recurrence occurred after receiving a kidney transplant. The other three were not transplanted and there was no clear trigger for the recurrence.

Four patients had specific features of glomerulonephritis (Table 1): Patient 5, C3GN type, carries a complement gene alteration. She is currently under eculizumab treatment, with normal renal function (sCr 0.77 mg/dL) and without proteinuria; Patient 12, IC-MPGN type, carries a complement gene alteration. She was treated with plasmapheresis, has normal renal function (sCr 0.68 mg/dL), but presents proteinuria of 3.89g/day; Patient 15, C3GN type, carries no genetic abnormalities, she is under eculizumab treatment, presenting sCr 1.3 mg/dL and proteinuria of 0.95g/day; finally, Patient 4, C3GN type, carries no genetic abnormalities. She developed it “*de novo*” in the transplanted kidney and was the cause of the graft loss. Four patients had a low C3, but only one of them belong to this group having GN.

Follow up of patients treated versus not treated with eculizumab:

Three of the ten patients treated with eculizumab (30%) required hemodialysis at the time of the P-aHUS episode, but all 3 recovered renal function. None of the eculizumab treated patients reached ESRD at the end of the follow up. In contrast, within the group of patients who did not receive eculizumab (12 patients), 50% required hemodialysis at onset. Four of the 12 patients (33%) reached ESRD during the first month and six patients (50%) required RRT at the end of the follow up (Figure 2). Eculizumab was suspended in 7 of the 10 cases after a median time of 10 months of treatment (6-10 IQR). Two of them were carriers of pathogenic variants. Whilst no recurrences were observed during the treatment, two of the patients, one carrying a genetic defect, had a recurrence 5 and 7 months after eculizumab discontinuation, respectively.

Five additional cases received eculizumab with posterity to the P-aHUS event. In two cases, both carrying complement pathogenic variants, eculizumab was used as prophylaxis for a kidney transplant. None of them had a recurrence of aHUS and both patients are still receiving eculizumab. In a third case, it was used to successfully treat a relapse of aHUS after transplantation. She does not carry complement genetic or acquired defects. Eculizumab was also used to treat the recurrences after eculizumab discontinuation of the two P-aHUS mentioned above. At the time of writing this report they remain on treatment.

DISCUSSION

In this study we describe the epidemiological, clinical and prognostic data of 22 P-aHUS patients from the Spanish cohort, with a median follow up time of 7.9 years/patient to illustrate that there are no significant differences between these group of patients and the non-pregnancy related aHUS patients. We describe the complement abnormalities in the aHUS candidate genes found in 41% of our patients and discuss their role in P-aHUS pathogenesis. An interesting observation is that C-section shows an association with P-aHUS in our cohort. Finally, we report an excellent experience with the use of Eculizumab, compared to plasma treatments. Our findings together with those generated from other P-aHUS cohorts should improve prevention, diagnosis and treatment of P-aHUS patients.

P-aHUS is a serious condition that has been associated with an elevated morbidity for the mother and, in pre-partum cases, also high morbidity/mortality for the fetus.¹⁶ In our series (n=22), one third (33%) of the twelve cases who were not treated with eculizumab reached ESRD during the first episode and half (50%) of the patients within this subgroup required RRT at the end of the follow up. This is consistent with previous data by the French group, who reported 62% of the patients reaching ESRD during the first month and 76% requiring RRT at the end of the follow up.² Our relatively reduced percentage of cases with poor evolution compared to the French cohort may be due to the fact that in our series approximately 50% of the cases, likely those with more severe disease presentations, were treated with eculizumab. Interestingly, two patients (9%) had a previous history of unexplained abortions, perhaps related to P-aHUS episodes, without pathological consequences for the mother.

A complete, state of the art, genetic and molecular analysis was performed in all patients to search for inherited and acquired complement abnormalities. These analyses resulted in the identification of confirmed pathogenic variants in 9 (41%) of them. Interestingly, no carriers of mutations in MCP (CD46) or anti FH auto antibodies

were present in our cohort. Consistent with previous findings in the general aHUS population and in the French P-aHUS series, most patients in our cohort carry mutations that impair factor H regulation.² Of note, the allele frequency of both at risk aHUS haplotypes (*CFH*-H3 and *MCP*_{ggaac}) were significantly elevated in our P-aHUS cohort, further supporting that individuals developing P-aHUS present a significant genetic predisposition involving both rare pathogenic mutations and common risk polymorphisms¹⁷ (Table 2). The percentage of carriers of pathogenic variants in our P-aHUS cohort (41%) is similar to that of the whole aHUS Spanish cohort (39%; n= 280), but is notably smaller than that the 86% reported previously for the French cohort. This reduced frequency of genetic abnormalities in our series cannot be attributed to differences in the clinical criteria for inclusion or to the severity of the disease. Similarly, it cannot be argued that is the result of an incomplete genetic or molecular analysis of the patients. Being as it may, we interpreted this data as a confirmation that pregnancy and postpartum complications represent both a direct cause of TMA and a very strong aHUS triggering factor in those individuals carrying pathogenic complement variants.

It has been suggested that the second pregnancy is the situation with the highest P-aHUS risk.² In contrast, in our cohort the first pregnancy was the time for the onset of P-aHUS in 73% of our patients. The percentage of patients carrying pathogenic variants was similar in both groups. Similarly, we did not found a significant difference between carriers and non-carriers of pathogenic variants in the number of prior normal pregnancies that ended without complications, although the frequency of previous abortions was increased in the group of women carrying mutations (Table 3). This is in agreement with the data from the French cohort. In contrast, none of our patients had a clear diagnosis of preeclampsia or HELLP syndrome and none had a familial history of aHUS.

We observed no differences between carriers and no carriers of mutations regarding the percentage of patients with recurrences, although the time to the first

recurrence was shorter in those cases carrying genetic alterations (Table 3).

From an immunological point of view a normal pregnancy requires an exquisite balance that allows an immune tolerance between the mother and foetus, preserving the immune defence against pathogens. It has been shown that alterations of this balance result in adverse pregnancy outcomes like preeclampsia, HELLP syndrome, recurrent abortions or intrauterine growth restriction. Complement dysregulation in particular, has an essential and causative role in damaging this foetal-placental unit.¹⁸⁻²⁴ This seems to agree with our observation that some patients carrying complement pathogenic variants in our cohort, and in the French cohort reported previously, had a history of abortions.

The delivery time has been described as that of highest risk of complement dysregulation due to the subsequent inflammation, the bleeding and the potential infections. Fakhouri *et al*, based on the type of mutations they found in their P-aHUS cohort, have suggested that the postpartum period probably requires a tougher control of complement activation on the fluid phase.² This is in agreement with our observation that the predominant genetic alteration associated with P-aHUS impairs mostly the functionalities of the fluid phase regulator factor H.

A remarkable finding was the elevated percentage of C-section in the subgroup of patients within our P-aHUS cohort who presented in the postpartum period (81%). C-section involve a higher endothelial damage, heavier bleeding and an increased risk of infections than vaginal deliveries. Three of our patients had, in addition, a documented excessive bleeding. Of interest, none of the women with previous deliveries have had a C-section, which could be interpreted the C-section being a strong trigger of TMA. If this is confirmed in futures studies, patients with strong predisposition to aHUS should perhaps be followed very closely in case they may require C-section.

Distinguishing P-aHUS from preeclampsia and HELLP syndrome is always a challenge. However, there are several data that help in the differential diagnosis (See

Methods). As illustrated in Table 1, haemolytic anemia, thrombocytopenia and renal function deterioration were remarkably severe in our patients and, with only two exceptions, serum creatinine at diagnosis was higher than 1.5 mg/dL. Patients with or without genetic complement alterations were clinically undistinguishable and, most important, all of them showed no improvement after delivery. Their responses to eculizumab were also identical and positive in all cases. Based on all these, we are confident that our patients are well diagnosed of P-aHUS.

In agreement with several previous reports, our data illustrate that plasma treatments were unsuccessful in the majority of the patients. In our series only 3 out of seventeen patients who were treated with plasmapheresis had a renal response (18%). Additionally, 2 out of 3 patients who received fresh frozen plasma had a renal response. These non-responses or incomplete responses to plasma treatment contrast with the excellent responses to eculizumab in all treated patients in our series.

Eculizumab is a humanized monoclonal antibody that prevents cleavage of the C5 molecule, blocking activation of the terminal pathway and the formation of the membrane attack complex (C5b-9). Although its efficacy in the treatment of aHUS has been demonstrated in numerous studies,^{6-8,25-28} there are only limited reports describing its use in P-aHUS.²⁹⁻³⁷ Our P-aHUS cohort is the first one to include a significant number of cases treated with eculizumab (n=10). Notably, the eculizumab treatment was successful, with normalization of all hematological parameters and preservation of renal function, in all cases. None of the patients required RRT (dialysis or transplantation) at the end of the follow up, despite 3 of the 10 patients (30%) required acute hemodialysis prior to initiate the eculizumab treatment. In addition to these 10 patients, five additional cases were successfully treated with eculizumab, to prevent recurrences after a kidney transplantation (two patients, carriers of complement mutations) or to treat relapses (one patient after transplantation and two patients 5 and 7 months after discontinuation of the eculizumab treatment, respectively; one of these

three last patients was a carrier of a complement pathogenic variants). As a whole, our study illustrates the complete efficacy of eculizumab to treat P-aHUS in 13P-aHUS patients (two were treated twice), without any adverse situations reported in any of them.

Eculizumab was discontinued in 7 of the 10 treated cases after a median time of ten months of treatment (6-11 IQR), including two who were carriers of pathogenic variants. One of these cases with a genetic alteration had a recurrence after 7 months after being taken off treatment. No recurrence was observed in the other yet, but follow up time after discontinuation is still short (481 days). One of the patients without genetic defect also had a recurrence after 5 months of eculizumab discontinuation. Both patients were successfully treated restoring the eculizumab. It should be noted that, in the case without genetic alterations who had the recurrence after eculizumab discontinuation, a renal biopsy showed C3GN in addition to the TMA lesions, and she had the aHUS onset at 32 weeks of gestation.

In previous studies of pregnant women treated with eculizumab (Paroxysmal nocturnal hemoglobinuria (PNH) and aHUS cases) no adverse situations were reported in the fetus. Eculizumab has never been found in the milk of the treated mothers and only small amounts of eculizumab were found in cord blood in a small percentage of cases.³⁸⁻⁴¹ In our cohort the drug was administered only to one patient during pregnancy without any adverse consequences.

The limitations of our study are those related to ultra-rare diseases like aHUS, their retrospective nature and the relatively small size of our cohort, which despite representing the whole Spanish populations and covering almost 30 years limits the power of the statistical analysis.

In summary, our study illustrates that P-aHUS is a severe disease with an elevated morbidity. In our cohort, less than half of the patients (41%) carry a clear genetic predisposition to aHUS and the disease presents more frequently during the

first pregnancy. We confirm that the postpartum period is the time with highest risk to develop the disease and suggest the C-section is associated with the onset of P-aHUS in our cohort. Finally, we report that eculizumab treatment has demonstrated efficacy in all treated patients in our cohort, illustrating the potential of this treatment to change the fatal renal function prognosis in P-aHUS. Further studies in other cohorts should confirm and extend our conclusions providing a better understanding of the disease and guidelines for an improved management of the P-aHUS patients, including criteria for an individualized long-term treatment with eculizumab.

METHODS

The aHUSC3G registry

The aHUS and C3G registry (<https://www.aHUSC3G.es>) is a registered clinical and basic research resource funded and supervised by the Centro de Investigación Biomédica en Red de Enfermedades Raras (Ciberer; www.ciberer.es). Ciberer belongs to the Instituto de Salud Carlos III, which depends on the Spanish Ministry of Health. The aHUSC3G registry was launched in 2013 to preserve the clinical, genetic and laboratory data of aHUS and C3G Spanish patients generated by the Working Group on Complement and Renal Disease at the Centro de investigaciones Biológicas and Hospital Universitario La Paz, and to facilitate their analysis by clinical and basic researchers.

Study Population, definitions and treatments

Patients with P-aHUS were identified in 13 Spanish hospitals over the 1981-2017 period. P-aHUS was defined as aHUS during pregnancy or puerperium. The latter considered as the period from birth to 8 weeks postpartum. A diagnosis of aHUS was considered in patients who fulfilled the following criteria: platelet count $<150 \times 10^9/L$ or decrease of $> 25\%$ from baseline values, haemolytic anaemia and serum creatinine level greater than upper limit of normal range, together with a negative Coombs test, normal activity of ADAMTS-13 and negative Shiga Toxin.⁴² In the differential diagnosis between preeclampsia, HELLP syndrome and P-aHUS, preeclampsia was defined by a systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg after 20 weeks of gestation in a previously normotensive patient and proteinuria ≥ 0.3 g/day, or, in the absence of proteinuria, by the detection of new-onset hypertension after 20 weeks of gestation together with any of the following data: platelet count $< 100,000/10^9/L$, serum creatinine > 1.1 mg/dL, liver transaminases at least twice the

upper limit of the normal concentrations, pulmonary edema, and cerebral or visual symptoms. HELLP syndrome was defined by the presence of microangiopathic haemolytic anemia, platelet count $\leq 100,000/10^9/L$, total bilirubin $\geq 1.2 \text{ mg/dL}$ and serum aspartate aminotransferase levels > 2 times above the upper limit of the normal range.⁴³ Eculizumab was administered in all treated patients intravenously at a dose of 900 mg per week for four weeks, and then 1200 mg every two weeks. Plasmapheresis was discontinued in all the patients once they started eculizumab. All the patients received anti meningococcal vaccination and received antibiotic prophylaxis according to label instructions. The duration of eculizumab therapy was decided by the treating physician, based on the patient's response and individual characteristics. Data were compiled from the medical records of the participating centers using a uniform protocol. Follow-up period was defined as the interval between the P-aHUS onset and the last visit or death.

The studies reported here have Institutional Review Board's approval. Informed consent was provided to all individuals participating in the study, according to the Declaration of Helsinki. The Public Health System pays eculizumab treatments in Spain. None of the agencies funding the present work are responsible for the payments of the eculizumab treatment of the patients included in this report.

Outcomes

The primary outcome was the hematologic and renal responses. Hematologic response was defined by the normalization of platelet count and disappearance of all the markers of MAHA (low hemoglobin, elevated LDH, decreased serum haptoglobin and the presence of schistocytes in peripheral blood examination). Renal response was defined by the recovery of renal function with $\geq 25\%$ reduction in serum creatinine levels (during the acute renal failure) in two consecutive measurements for ≥ 4 weeks. Secondary outcome was to reach end stage of renal disease (ESRD), defined as the

need of renal replacement therapy (RRT), either dialysis or transplantation.

Statistical analysis

Continuous variables are shown as median and inter quartile range [IQR] (25th and 75th percentile). Categorical variables are shown as frequencies and percentages. Categorical variables were compared with Chi-square test, with Yate's correction if necessary. Time to first recurrence was estimated by Kaplan Meier, censoring the data on the end-of-follow-up date if the patient had not experienced any recurrence; it is displayed as mean and confidence interval or median if it is available. The comparison between groups has been performed with the log-rank method. Mean follow-up time was calculated as the average of the sum time accumulated by each patient. The average follow-up in patients treated or not with eculizumab from the aHUS onset to RRT or censoring time, was estimated by Kaplan Meier. All p-values were two-tailed and values less than 0.05 were considered statistically significant. Statistical analyses were performed using SPSS version15 (StataCorp, TX, USA).

Disclosure

Conception, design, data collection and analysis, as well as writing of the study were performed by investigators with no support from pharmaceutical companies. AH, EA, JP, MC, JM, TC, ME, MC, MP and SRdC have received honoraria from Alexion Pharmaceuticals for giving lectures and participating in advisory boards. None of these activities has had any influence on the results or interpretations in this article. Other authors declare no conflicts of interest. The results presented in this paper have not been published previously in whole or part.

Acknowledgements

We are in debt to all patients and relatives participating in this study. Work in this report was funded by the Instituto de Salud Carlos III: REDinREN (RD016/009 and RD012/0021) and Fondo de Investigaciones Sanitarias (ISCIII/FEDER) ref 13/02502 and ref 16/01685. SRdeC is supported by the Spanish “Ministerio de Economía y Competitividad-FEDER” (SAF2015-66287R), the Seventh Framework Programme European Union Project EURenOmics (305608) and the Autonomous Region of Madrid (S2010/BMD-2316). SRdeC is member of the "CIB Intramural Program “Molecular Machines for Better Life” (MACBET)". This work was developed under the supervision of the Spanish Registry of the atypical Hemolytic Uremic Syndrome and C3 Glomerulopathy (aHUS/C3G) registry”.

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Figure legends

Figure 1. Timing of onset of the P-aHUS event.

Black circles represent patients carriers of complement pathogenic variants and white circles non-carriers of genetic alterations.

Figure 2. Renal survival

Kaplan-Meier curves for renal survival at 24 months in patients treated and non treated with eculizumab ($p < 0.05$)

TABLE 1. Clinical Characteristics

Patient	CCM	Dgn aHUS before	Previous pregnancies, via	*Age	*Time of onset	*Type of birth	*Hb min (g/dl)	*Plaq min (x10 ⁹ /L)	*LDH max mg/dl	*sCr max mg/dl	*Renal biopsy	*Eculizumab	*Other therapies	Outcome
1	No	No	No	37	11 dPP	Cs	NA	NA	NA	HD	No	No	No	ESRD. Lost RT due to relapse. Exitus.
2	No	No	No	21	5 dPP	Cs	6.9	30	2616	HD	No	No	FFP	CR
3	No	Yes	No	24	7 dPP	Vd	5.1	170	370	1.8	TMA	No	No	ESRD. RT.
4	No	No	No	34	6 wPP	Vd	6.9	66	934	HD	TMA ^a	No	PE, CC, CP	ESRD. Lost 1st RT due to C3GN. Relapse in 2nd RT with response to eculizumab
5	Yes	No	No	38	2 dPP	Cs	7.5	21	3338	2.3	C3GN	Yes	PE	CR
6	Yes	No	1FTP,Vd	41	4 wPP	Cs	5.3	60	1977	HD	No	No	PE	ESRD. Lost 2 RT due to relapse. 3rd RT with prophylaxis
7	Yes	No	No	21	5 dPP	Cs	5.9	40	4162	HD	TMA	No	PE	ESRD Lost RT due to relapse.
8	No	No	No	42	4 dPP	Cs	6.3	52	2450	HD	TMA	Yes	PE	CR
9	No	No	2FTP,2Vd	28	1 dPP	Vd	8.7	26	1354	4.2	TMA	No	Heparin	CR
10	No	No	1FTP,1Vd	37	1 dPP	Cs	7.5	40	887	5.5	No	No	PE, FFP	CR
11	No	No	No	35	1 dPP	Cs	5.3	26	7487	HD	No	Yes	PE	CR
12	Yes	Yes	1A	38	36 WG	Cs	8.1	49	867	1.09	TMA, IC-MPGN	No	PE	CR ^b
13	No	No	1FTP,1Vd	28	36 WG	Vd	8.2	41	455	4.23	TMA	Yes	PE	CKD
14	No	No	No	35	19 WG	(A)	8.9	65	340	1.4	No	No	No	CKD
15	No	Yes	No	32	32 WG	Vd	7.8	66	511	2.9	TMA, C3GN	Yes	PE	Relapse ^c ; CKD
16	Yes	No	No	33	7 dPP	Cs	4.5	50	3373	HD	No	No	PE	ESRD. RT with prophylaxis.
17	No	No	No	28	1dPP	Cs	5.2	20	7183	4.55	No	Yes	PE,FFP,C C	CR

18	Yes	No	2A	40	36 WG	Cs	4.7	53	2252	HD	TMA	Yes	PE	CKD
19	Yes	Yes	No	24	19 WG	Cs	7.3	64	879	3.5	No	Yes	No	Relapse ^c ; CKD
20	No	No	No	25	2 dPP	Cs	7.1	98	1407	3.8	No	Yes	PE	CR
21	Yes	No	No	25	9 dPP	Cs	5	16	4055	4.3	No	No	PE	Relapse, CKD
22	Yes	No	No	39	7 dPP	Cs	7.1	80	2600	3.2	TMA	Yes	PE	CR

* Data at the P-aHUS event; ^a and a “de novo” C3GN in Renal transplant ; ^b C3G with normal renal function and proteinuria of 0.95 g/day ; ^c after eculizumab discontinuation, and the relapse was retreated with eculizumab, with response.

Code = patient, CCM = carriers of pathogenic variants in complement of mutation, dPP = day postpartum, wPP = week postpartum, WG = week of gestation, FTP = Full Term Pregnancy, A = Abortion, Vd = Vaginal delivery, Cs = caesarean section, NA = Not available, HD = hemodialysis, IC-MPGN = immune complex-mediated membranoproliferative GN, PE = plasma Exchange, FFP = fresh frozen plasma, CC = corticosteroids, CP = cyclophosphamide, RT = renal transplant, CR = complete remission, CKD = Chronic kidney disease.

TABLE 2. Complement levels, genetics and auto antibodies in patients with postpartum aHUS

Patient	Genes analyzed (1)	Pathogenic variants	CFH risk haplotype	MCP risk haplotype	Anti FH/FI antibodies	C3 75-135mg/dl	C4 14-60mg/dl	FH 90-302µg/ml	FI 71-115%	MCP 91-109%
1	CFH, MCP, CFI (Sanger)	None	Hom (H3, H3)	Hom	No	104	19	146	87	ND
2	NGS panel (Ion Torrent)	None	No (H2, H4b)	Hom	No	ND	ND	247	ND	110
3	CFH, MCP, CFI,CFB (Sanger)	None	Het (H3, H4b)	No	No	92	15	132	69	100
4	CFH, MCP, CFI,CFB,C3,THBD (Sanger)	None	Het (H3, H4a)	No	ND	ND	ND	ND	ND	ND
5	NGS panel (Illumina)	C3: Exon 4; c.481C>T; p.R161W	Hom (H3, H3)	Het	No	87	16	79	97	100
6	CFH, MCP, CFI (Sanger)	CFI: Exon 3; c.452 A>G; p.N151S	Hom (H3, H3)	Het	No	83	25	199	42	103
7	CFH, MCP, CFI, CFB, CFHR1 (Sanger)	CFHR1: p.L290S, A296V (CFHR1:CFH hybrid gene)	Hom (H3, H3)	No	No	64	29	102	100	97
8	CFH, MCP, CFI (Sanger)	None	Hom (H3, H3)	Hom	No	94	32	248	ND	ND
9	CFH, MCP, CFI,CFB,C3,CFP,THBD (Sanger)	None	Het (H3, H5)	Het	No	106	26	197	113	ND
10	CFH, MCP, CFI,CFB,C3,CFP,THBD (Sanger)	None	Het (H3, H4a)	Het	No	104	10	105	109	ND

11	NGS panel (Illumina)	None	No (H4a, H4a)	Hom	No	93	10	138	99	88
12	<i>CFH, MCP, CFI</i> (Sanger)	<i>CFH: Exon2; c.157C>A; p.R53S</i>	Het (H3, H2)	Hom	No	137	28	242	100	ND
13	NGS panel (Ion Torrent)	None	No (H4a, H4a)	No	No	71	23	174	93	97
14	NGS panel (Ion Torrent)	None	Het (H3, H1)	No	No	82	13	122	70	130
15	<i>CFH, MCP, CFI, CFB, C3, CFP, THBD</i> (Sanger)	None	Het (H3, H4a)	Hom	No	51	22	45	113	100
16	<i>CFH, MCP, CFI, CFB</i> (Sanger)	<i>CFH: Exon 16 c.2284G>T; p.E762*</i>	No (H1, H5)	Het	No	63	30	85	93	125
17	<i>CFH, MCP, CFI</i> (Sanger)	None	No (H1, H4a)	No	No	106	42	147	120	100
18	NGS panel (Illumina)	<i>C3: Exon 41; c.4855A>C; p.S1619R</i>	Het (H3, H1)	No	No	102	40	177	90	119
19	NGS panel (Ion Torrent)	<i>CFHR1: p.L290S, A296V</i> (<i>CFHR1:CFH hybrid gene</i>)	Het (H3, H1)	Hom	No	99	20	99	100	ND
20	NGS panel (Ion Torrent)	<i>CFHR1: p.L290S, A296V</i> (<i>CFHR1:CFH hybrid gene</i>)	Het (H3, H1)	No	No	91	12	105	100	123
21	NGS panel (Illumina)	<i>CFH: Exon13; c.1707C>A; p.C569*</i>	No (H1, H7)	No	No	129	27	220	116	104
22	NGS panel (Illumina)	None	No (H1, H1)	No	No	141	38	333	97	113

(1) NGS panel (Ion Torrent) includes the *CFH, CFI, MCP, C3, CFB, THBD, ADAMTS13, DGKE, CFHR1, CFHR2, CFHR3, CFHR4, CFHR5* and *CFP* genes. NGS panel (Illumina) interrogates as many as 48 genes and includes all complement genes.

(2) We consider variants of uncertain significance those with unknown functional consequences or unknown relationship with aHUS.

TABLE 3. Comparison between carriers and no carriers of complement pathogenic variants.

	Total (n=22)	Carriers (n=9)	No carriers (n=13)	p
Family history of aHUS	0	0	0	
Diagnosis of aHUS before this event	2	2 (22%)	2 (15%)	0.7
Previous pregnancies	6	3 (33%)	3 (23%)	0.6
Not complicated previous pregnancies	4	1 (11%)	3 (23%)	0.5
Previous complicated pregnancies:				
Abortion	2	2 (22%)	0 (0%)	0.8
Preeclampsia/HELLP	0	0	0	
Prepartum	6	3 (33%)	3 (23%)	0.6
Postpartum	16	6 (67%)	10 (77%)	0.6
Caesarea	13	6 (67%)	7 (54%)	0.6
Severe bleeding	3	1	2	0.6
Fulfill also criteria of Preeclampsia?	17	7 (78%)	10 (77%)	1.0
Fulfill also criteria of HELLP syndrome?	7	3 (33%)	4 (31%)	0.9
Acute hemodialysis required?	9	3 (33%)	6 (46%)	0.6
RRT* at the end of follow up	6	3 (33%)	3 (23%)	0.6
Eculizumab treatment	10	4 (44%)	6 (46%)	0.10
Discontinuation of eculizumab	7	2 (50%)	5 (83%)	NS
Total patients with relapses	7	4 (44%)	3 (23%)	0.3
Relapses in the group treated with eculizumab	2	1	1	0.7
Average time till the first relapse (months) (<i>mean</i>)		44.5 [17.6-71.4]	305.0 [198.4-411.6]	0.05

*RRT = renal replacement treatment

Cumulative renal survival (%)