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Original Research Paper

Gynaecology

PREGNANCY-ASSOCIATED ATYPICAL HEMOLYTIC-UREMIC SYNDROME

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ABSTRACT

Pregnancy is associated with various forms of thrombotic microangiopathy, including hemolytic uremic syndrome. Atypical haemolytic uraemic syndrome is one of the main variants of thrombotic microangiopathy, and is characterised by excessive complement activation in the microvasculature. Pregnancy-associated atypical hemolytic-uremic syndrome (p-aHUS) is a rare condition characterized by microangiopathic hemolytic anemia, thrombocytopenia, and acute kidney injury. Triggered by pregnancy, genetically predisposed women develop the syndrome, leading to a disastrous hemolytic disease characterized by diffuse endothelial damage and platelet consumption [1].

Being one of the differential diagnoses of preeclampsia–eclampsia and HELLP syndrome the clinician must be familiar with the disease due to its high mortality, which can be modified with early diagnosis and comprehensive treatment. The authors have here reported a case of atypical haemolytic uremic syndrome diagnosed postnatal.

KEYWORDS : atypical haemolytic uraemic syndrome, thrombotic micrangiopathy, pregnancy

BACKGROUND:

Atypical haemolytic uraemic syndrome (aHUS) is a variant of the thrombotic microangiopathy which is characterised by the following clinical triad: non-autoimmune haemolytic anaemia, thrombocytopenia and acute kidney failure [2,3]. When pregnancy triggers the thrombotic microangiopathy (TMA), the disease is referred to as pregnancy-associated atypical hemolytic-uremic syndrome (p-aHUS).

Traditionally, haemolytic uraemic syndrome is classified in 2 ways:

Typical haemolytic uraemic syndrome which is more common in children and is associated with a prior infection from Shiga toxin-producing Escherichia coli (STEC) and presence of Shiga toxin causing endothelial damage and complement activation [5]and Atypical haemolytic uraemic syndrome which in 50–60% of cases is characterised by an irregularity of the complement system, caused by genetic mutation of its inhibitors [4], which in the majority of patients leads to terminal chronic kidney failure and the need for a kidney transplant.[6, 7, 8]

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 [7, 8]. 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 [9].

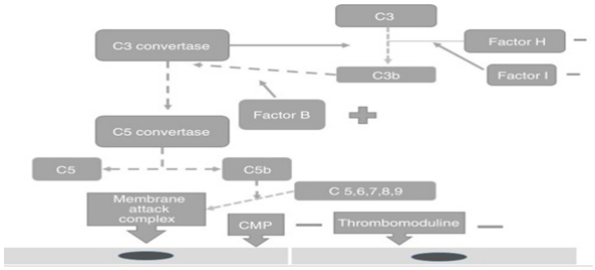
EPIDEMIOLOGY :

There are reports of an incidence of atypical haemolytic uraemic syndrome of 2 cases for every 1,000,000 inhabitants. 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. The clinical course of aHUS can be severe, with most patients suffering neurologic injury, renal impairment, and multiorgan failure [2,3]. In a French cohort, 60 to 70% of aHUS developed end-stage renal disease (ESRD) [12].

PATHOPHYSIOLOGY:

A genetic mutation in complement regulatory genes has been identified in approximately 60 percent of patients with aHUS [7,8]. Dysregulation of the complement system leads to endothelial, neutrophil and platelet activation causing TMA associated with hemolytic anemia and thrombocytopenia, which in turn may cause severe organ damage in multiple vital organs [13]. The excessive activation of the complement pathway results from dysfunction of regulatory proteins secondary to mutations in the FCH, PCM, or C3 genes [4].

Figure: Complimentary Pathway



Richard and Buddles 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. 1). Richards[14] 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 replacement S206P, in the familial 2 (heterozygote) and 3 (homozygote), which confirmed that the deregulation of the complement predisposes the development of thrombotic microangiopathy and that patients under review for these defects could provide preventative treatment strategies in patients with this type of mutation [18]. The FCH mutation occurs in 6–20% of patients with atypical haemolytic uraemic syndrome and the mutation in CD46 in 10% of patients.[14, 15, 16]

Factor I is an inhibitor of all complement pathways. It has the capacity to degrade C3b and C4b activated proteins in the present of cofactors such as FCH, CD46, among others. Incomplete deficiency of factor I is also associated with the development of atypical haemolytic uraemic syndrome.

The increase in the function of the complement system factors, such as factors B and C3 may also cause the expression of this syndrome.[15,16]

Autoantibodies against FCH increase the risk for its expression but the disease has an associated incomplete penetration which is different to each mutation and therefore not all carriers of mutations will develop atypical haemolytic uraemic syndrome,[16] only those women with a genetic predisposition and an external trigger.

Atypical uraemic haemolygic syndrome and pregnancy

P-aHUS is a severe systemic disease. Hyperactivation of complement results in diffuse endothelial injury with subsequent formation of fibrin and platelet microthrombi in the vasculature leading to hemolysis, thrombocytopenia, and end organ dysfunction from ischemia (mostly in the form of acute kidney injury). The pathogenesis of atypical haemolytic uraemic syndrome in pregnancy remains uncertain, it appears in 21% of adult women and in 79% of them it presents during the postnatal period [1]. Several factors such as inflammation, drugs, cancer, preeclampsia, maternal–fetal hemorrhage, and infections may act as a trigger for complement activation in an already genetically susceptible individual.

CASE:

A 33-year old G4P2L2A1 woman was admitted to our facility at 36 weeks of gestation with complaints of bleeding per vagina with passage of clots for 1 hour duration. On admission, she had elevated blood pressure of 180/100mmHg and urine albumin 3+. She was in active labor, per abdomen was tense and fetal heart sound could not be heard n doppler or stethoscope. Provisional diagnosis of possible Abruptio Placentae with IUFD was made. The patient underwent spontaneous vaginal delivery. On postpartum day 1, the patient developed severe thrombocytopenia, haemolytic anemia, elevated liver enzymes, and acute kidney injury. She was subsequently treated for suspected HELLP syndrome.

Laboratory investigation revealed serum creatinine of 2.1mg/dl rising to 5.3mg/dl and then plateauing, haemoglobin 5.7g/dl, lactate dehydrogenase >4670 U/L, serum aspartate aminotransferase 119 IU/L, total bilirubin 1.89 mg/dl, platelet count 80,000/mm3. Peripheral smear revealed marked schistocytosis. The patient's condition did not improve during the first 24 hours postpartum. With the presence of TMA, ADAMTS13 levels were sent. Plasma exchange was still not initiated. From day 3 of hospitalisation gradual rise of serum creatinine was noted with haemoglobin falling to 4.9g/dl and platelets to 47,000. Patient was transfused with 1 pint packed cells and 2 pints fresh frozen plasma but plasma exchange was still not initiated. On hospital day 5, laboratory values started to improve. On hospital day 8, the ADAMTS13 activity was reported as normal at 95%. Complement tests revealed alternative pathway dysregulation with low plasma levels of C3 at 70mg/dl (86-184mg/dl) and low levels of C4 11mg/dl (20-59mg/dl).

A diagnosis of aHUS was considered due to anemia and thrombocytopenia persisting even after termination of pregnancy. Further genetic workup revealed the patient to be a heterozygous carrier for a CD46 (MCP membrane cofactor protein) sequence variant (p.T383I; c.1148C > T). Mutations in CFH, CFB, C3, and CFI genes were excluded. The patient didn't require dialysis and was discharged on day 15 of admission with a creatinine value of 1.9mg/dl. The patient received vaccination against *Neisseria meningitides*, *Streptococcus pneumoniae*, and *Haemophilus influenzae* before being discharged in anticipation of Eculizumab administration.

Eculizumab was started 27 days after discharge at a dose of 900 mg intravenously per week for 4 weeks with a maintenance regimen of 1,200 mg at week 5 followed by 1,200 mg every 2 weeks for 26 weeks. The drug was well tolerated, without developing the associated side effects of headache, leukopenia, or allergic reactions. Currently, the patient, in clinical remission, is on Eculizumab treatment and doing well.

DIFFERENTIAL DIAGNOSIS:

The diagnosis of p-aHUS can be challenging, as this condition mimics several other diseases that must be ruled out when making a diagnosis. Common features such as acute renal failure, thrombocytopenia, and microangiopathic hemolytic anemia seen in p-aHUS are also observed in severe preeclampsia with HELLP syndrome, TTP, and acute fatty liver of pregnancy. Although it is sometimes difficult to distinguish between these syndromes, it is imperative to make the right diagnosis in a timely manner to treat patients appropriately. HELLP syndrome typically resolves after delivery and hemolysis is less severe; note that it may act as a stimulus for the development of the p-aHUS in genetically predisposed patients. While some of the clinical features of these different syndromes overlap, different laboratory studies can help guide the clinician to the right diagnosis (Table 1).

	HELLP	AFLP	TTP	aHUS
Time of onset	3rd trimester	3rd trimester	2nd &3rd trimester	
Recovery after delivery	1wk	1-2d	No recovery	No recovery
Primary/ unique clinical manifestation	Hypertension and proteinuria	Nausea, vomiting, malaise	Neurological symptoms	Renal involvement
DIC (%)	less than 20	50-100	Rare	Rare
Acute kidney injury	Mild/ moderate	Moderate	Mild/ moderate	Severe
Lab findings				
Haemolytic anemia	+	0/+	++	+
Partial thromboplastin time increase	0/+	+	0	0
Hypoglycaemia	0	+	0	0
Thrombocytopenia (<100,000/mm3)	More than 20,000	More than 50,000	20,000 or less	More than 20,000
LDH (IU/L)	600 or more	Variable	More than 1000	More than 1000
Elevated ammonia	0/+	+	0	0
Elevated bilirubin	0/+	+	+	NA
Liver transaminase increase	+	++	0	0
vWF multimers	0	0	+	+
ADAMTS13 <10%	0	0	++	+
Clinical signs/symptoms				
Purpura	0	0	+	0
Fever	0	0	+	0
Neurological findings	0	0	+	0
Hypertension	+	0/+	0/+	+
Jaundice	0/+	++	0/+	0/+
Nausea and vomiting	0/+	0/+	+	+
Abdominal paim	0/+	0/+	+	+

Initial laboratory studies should include a haematic biometry to document anaemia and thrombocytopenia, the presence of fragmented cells in blood smears, to determine the presence of a high lactate dehydrogenase as part of the haemolytic anaemia study, the raising of creatinine, the determination of ADAMTS 13, and a stool test and PCR detection for *E. coli* 0157.

Complement gene mutations can be diagnosed by a comprehensive genetic and molecular study of the alternative complement pathway to confirm the diagnosis. Physicians also should be aware that complement gene mutation carriers, such as our patient, have penetrance of only 40 to 50%, and confer predisposition rather than causality. Hence, detection of these mutations should not be used to predict future recurrence of the syndrome but rather to emphasize physicians for close monitoring during pregnancy and the postpartum period.

Owing to its devastating nature, it is recommended to start Plasma Exchange (PE) within 24 hours of diagnosis without waiting for the aforementioned genetic testing or other testing (e.g., ADAMTS13), as genetic/confirmatory testing takes usually weeks before they are available but in our case we held PE as clinically the need didn't arise but PE helps in maintaining normal platelets counts and LDH. The abnormal pattern of complement activation and TMA are likely to persist with the risk of irreversible organ damage, primarily renal, in the subsequent weeks to months. Moreover, within 1 year of diagnosis, more than 60% of patients with acute kidney injury secondary to p-aHUS will progress to ESRD or succumb to the disease.

Eculizumab is a humanized recombinant monoclonal antibody that inhibits the terminal pathway of complement activation by blocking the activation of complement protein C5. Recent evidence among patients with p-aHUS suggests that Eculizumab increased platelet counts, improved renal function, decreased the need for renal replacement therapy, and improved overall quality of life. The latter has led the Food and Drug Administration (FDA) to approve eculizumab for the treatment for aHUS in the United States.

CONCLUSION : Diagnosis of p-aHUS is challenging, as it can mimic various diseases found during pregnancy and the postpartum. Plasma exchange can be held if patient is clinically stable but should be promptly initiated if clinical symptoms and degrading laboratory values. Eculizumab has risen to become an important tool to improve long-term comorbidities and mortality in this group population.

REFERENCES:

1. Pregnancy-Associated Atypical Hemolytic-Uremic Syndrome. AJP Rep. 2016 Mar; 6(1): e125–e128
2. C. Loirat, V. Frémeaux-Bacchi Atypical hemolytic uremic syndrome Orphanet J Rare Dis, 8 (2011), p. 60
3. F.C. Mohlin, S.C. Nilsson, et al. Functional characterization of 2 novel non-synonymous alterations in CD46 and a Q950H change in factorH found in atypical hemolyticuremic syndrome patients
4. Mol Immunol, 65 (2015), pp. 367-376 The long-term consequences of thrombotic microangiopathy (thrombotic thrombocytopenic purpura and hemolytic uremic syndrome) in pregnancy. Dashe JS, Ramin SM, Cunningham FG Obstet Gynecol. 1998 May; 91(5 Pt 1):662-8
5. Hemolytic uremic syndrome. Noris M, Remuzzi G J Am Soc Nephrol. 2005 Apr; 16(4):1035-50.
6. Bitzan M, Schaefer F, Reymond D. Treatment of typical (enteropathic) hemolytic uremic syndrome. Semin Thromb Hemost. 2010;36:594–610. doi: 10.1055/s-0030-1262881.
7. M. Blasco-Pelicano, S. Rodrıguez de Cordoba, J.M. CampistolSíndrome hemolítico urémico atípico Med Clin (Barc), 26 (2014), pp. 2-8
8. J.H. Brown, J. Tellez, V. Wilson, I.J. Macki, et al. Postpartum aHUS secondary to a genetic abnormality in factor h acquired through liver transplantation Am J Transplant, 12 (2012), pp. 1632-1636
9. M.A. Dragon-Durey, S.K. Sethi, A. Bagga, C. Blanc, et al. Clinical features of anti-factor H autoantibody-associated hemolytic uremic syndrome J Am Soc Nephrol, 21 (2010), pp. 2180-2187
10. T.H. Goodship, D. Kavanagh Pulling the trigger in atypical hemolytic uremic syndrome: the role of pregnancy J Am Soc Nephrol, 21 (2010), pp. 731-732
11. Hemolytic uremic syndrome in association with pregnancy B.S. Kaplan, R.S. Trompeter, J.L. Moake (Eds.), Hemolytic uremic syndrome and thrombotic thrombocytopenic purpura, Marcel Dekker, New York (1992), pp. 241-254
12. Pregnancy-associated hemolytic uremic syndrome revisited in the era of complement gene mutations. Fakhouri F, Roumenina L, Provot F, Sallée M, Caillard S, Couzi L et al. J Am Soc Nephrol. 2010 May; 21(5):859-6
13. Sallee M, Daniel L, Piercecchi MD, Jaubert D, et al. Myocardial infarction is a complication of factor H-associated atypical HUS. Nephrol Dial Transplant. 2010;25:2028–2032. doi: 10.1093/ndt/gfq160
14. Thrombotic microangiopathy focus on atypical hemolytic uremic syndrome Hematol Oncol Clin North Am, 29 (2015), pp. 541-559
15. Richards, E.J. Kemp, M.K. Liszewski, J.A. Goodship, et al. Mutations in human complement regulator, membrane cofactor protein (CD46), predispose to development of familial hemolytic uremic syndrome Proc Natl Acad Sci U S A, 28 (2003), pp. 12966-12971
16. Nilsson SC1, R.B. Sim, S.M. Lea, V. Fremeaux-Bacchi, A.M. BlomComplement factor I in health and disease Mol Immunol, 48 (2011), pp. 1611-1620