PREGNANCY-ASSOCIATED ATYPICAL HEMOLYTIC UREMIC SYNDROME (P-AHUS): COURSE, TRIGGERS, THERAPEUTIC APPROACHES AND ADVERSE PROGNOSTIC MARKERS

T.Kirsanova, M.Vinogradova

Federal State Budget Institution "Research Center for Obstetrics, Gynecology and Perinatology" Ministry of Healthcare of the Russian Federation, Moscow

PaHUS is a chronic, ultra-rare, life-threatening disease with uncontrolled complement activation, resulting in complement-mediated thrombotic microangiopathy(TMA), defined by the occurrence of microangiopathic hemolytic anemia and thrombocytopenia without ADAMTS13 deficiency. Triggered by pregnancy and another complement-amplifying conditions (CACs) women develop the syndrome, leading to a disastrous hemolytic disease characterized by diffuse endothelial damage and platelet consumption. This disease is a life-threatening condition that requires prompt diagnosis and therapy. An estimated incidence of P-aHUS is 1 in 25,000 pregnancies.

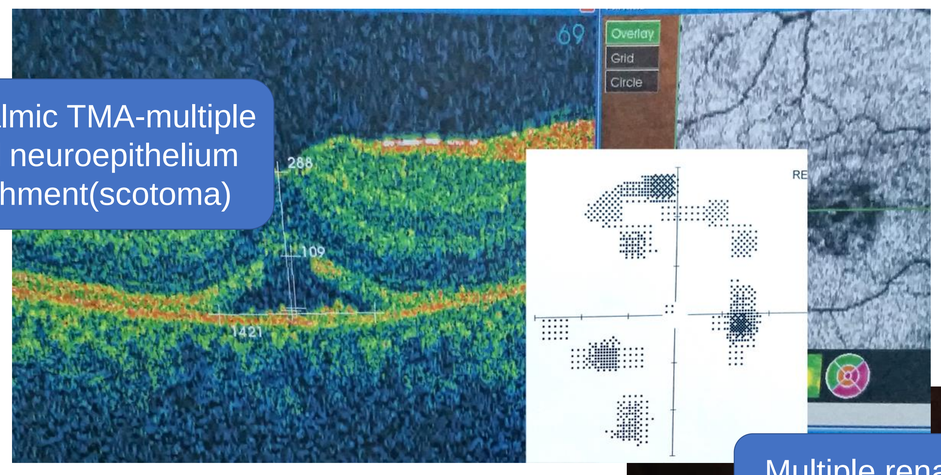
Aim: Analysis of CACs, course and adverse prognostic markers of obstetric aHUS..

Materials and methods: A retrospective analysis of P-aHUS treated or consulted in our center via telemedicine between 2013 and 01/2017. P-aHUS-diagnosed in cases with rapidly progressive after delivery or onset MAHAT without ADAMTS 13 deficiency and any others reasons of TMA

Clinical parameters	
Mean nadir platelet count*1000/mm3	38,5(4-128)
Mean nadir Hb, g/L	56,7(37-101)
LDH, IU/L	2584 (854-11360)
ALT/AST, IU/L	485,5/518
Peak creatinine, mkmol/l	485(150-1020)
PU, g/24h	3,7
Shystocytes,%	1,7
Outcomes	
Death	10 (32%)
End stage renal disease	6(19%)
CKD2-4	14(45%)
Recovery without CKD	1(3%)

Results:

Characteristic (n=31)	
Age, yers	30, 2 ± 8,0 (17-42)
Mean gestational age,weeks	35,2± 3,2
Clinical manifestation n(%)	
Before delivery	**20 (64%)**
-Preeclampsia(PE) signs/ HELLP onset	19/9 (61%/29%)
-gestational hypertension	1(3%)
After delivery	11(35%)
Triggered factors (CACs)	
PE/HELLP	19/9 (61%/29%)
Diarrhea(without STEC)	5(16%)
Hemorrhage 1000-2000ml	16(51%)
Manual removal of retained placenta	12(38%)
Previous pancreatitis	2(6%)
Others (fast-growing meningioma with surgical treatment; thrombocytosis, multiple fetal abnormalities)	3 (10%)
TMA	
Isolated acute kidney injury (AKI)	4(12%)
Gastrointestinal damage	22(70%)
• pancreatitis	11(35%)
• paresis	16(51%)
• ischemic colitis	7(23%)
• mesenteries thrombosis	1(3%)
Cardiac involvement	12(39%)
• Isolated reduced ejection fraction (EF<45%)	11(35%)
• high Troponin I-C(n=6)	6(19%)
• acute myocardial infarction	1(3%)
Erosion damage of the bladder	7(26)%
Acute Respiratory Distress Syndrome	17(55%)
Neurological	19(61%)
• Ischemic stroke	3(10%)
• Hemorrhagic stroke	1(3%)
• impaired consciousnes	19(61%)
Ophthalmic TMA-multiple retinal neuroepithelium detachment(scotoma)	7(23%)



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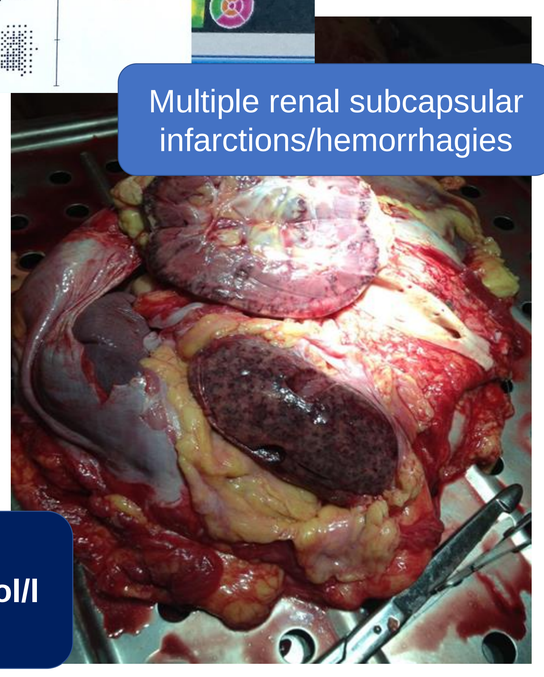

Multiple renal subcapsular infarctions/hemorrhagies

Consider the absolute platelet count and serum creatinine

n=31 PaHUS

Mean nadir platelet <30 000/mm3 n=16

Peak creatinine>200mkmol/l n=15

Only in "uncomplicated" case, a platelet count greater than 30 000 and SCr greater than 200 mkmol/l is highly unusual in TTP. All obstetrics cases are complicated with multiple CACS

n=10 PaHUS with 2 ways TMA

•multiorgan failure
•mechanical ventilation
•Hemodialysis
•urinary catheter
•central catheters

the intervals between the waves 4-39 days

Min Hb 52-101, g/L
Thrombocytes 4-100 000 mm/3
LDH 658-6600, Ед/л
Leucocytes 6-24

Min Hb 37-89, g/L
Thrombocytes 58-244 000 mm/3
LDH 2200-12600, Ед/л
Leucocytes 3,47-39

Only 6/31 had first pregnancy. Preeclampsia signs (PE) presented 3-18 days before P-aHUS manifestation, 10/31 had fetal death, 20/31-livebirth (27-38weeks). 10/31 with signs of severe PE or fetal death were urgency delivered. 7/31 had postpartum hemorrhage (blood loss1000-2000ml).6/31 had extirpation of uterus.19/31 required hemodialysis and 16/31 mechanical ventilation. All underwent therapeutic plasma exchange, 14/31 treated with eculizumab (4 of them died),therapy was started on 4-12 days, all of them appointed UFH or LMWH. All of patients who died had 2 "waves" of TMA: first TMA wave have damaged 2-5 organs without any proved infections (leukocytes were 6,7(3.7-7,8), all of them had a heart damage signs(EF22-42%), underwent hemodialysis, mechanical ventilation, urinary catheter which supposed to be a doors of superimposed infections. All of them were treated with combination of antibiotics agents (penicillin 8, tienam/meronem 8, cephalosporines 4, quinolones5).Second TMA wave was fatal. All of patients died from the superimposed septic disorders, resistant to antibiotic therapy.4 who received eculizumab therapy died 10-48 days after TMA onset, they had short improvement of hematological parameters. Patients who started eculizumab therapy had more severe disease at baseline with shorter history of PaHUS and responded well to eculizumab. 6 other patients with fatal outcome died from 2-7 days.

CONCLUSIONS: P-aHUS is a life-threatening multiorgan disorder associated with a significant mortality. HELLP/PE, non-STEC-diarrhea, hemorrhage and manual removal of retained placenta are the most often CACs.This analysis of organ involvement and CACs demonstrates a persistent risk of vital organ failure and mortality in patients with PaHUS after shortly improvement of hematological signs. They have increased risk of early second potential fatal TMA events due to superimposed infection. Antibiotic strategy should be worked out. The survival rate in the group receiving eculizumab was 71.4% (10 of 14), despite the fact that the timeliness of appointments and the usefulness of the courses is clearly not optimal, and of those who have not - 64,7% (11 of 17), in spite of possible maintenance and PE therapy.Thus, eculizumab reduced the risk of mortality

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Tatiana Kirsanova
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