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BRIEF REPORT

Atypical hemolytic uremic syndrome induced by SARS-CoV2 infection in infants with *EXOSC3* mutation

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Abstract

Background Atypical hemolytic uremic syndrome (aHUS) is a rare disease characterized by systemic thrombotic microangiopathy mainly in the kidneys and mostly due to genetic disorders leading to uncontrolled activation of the complement system. Severe complications of SARS-CoV2 infection are linked to microvascular injury and complement activation is suspected to play a role in the pathogenesis of endothelial cell damage in severe COVID-19.

Methods We present the first two cases of aHUS triggered by SARS-CoV-2 infection in two unrelated infants with the same mutation in the RNA exosome gene *EXOSC3*. This mutation is known to cause pontocerebellar hypoplasia type 1b, an autosomal-recessive neurodegenerative disease. So far, no kidney involvement in affected persons was reported.

Results As eculizumab treatment was unsuccessful and complement-mediated disorders were ruled out, we suppose that the atypical HUS in our two patients is not due to complement-mediated thrombotic microangiopathy but rather due to a dysfunction of the RNA exosome.

Conclusions The RNA exosome is crucial for the precise processing and degradation of nuclear and cytoplasmatic RNA. We suspect that the SARS-CoV-2 infection led to changes in RNA that could not be offset by the defective RNA exosome in our two patients. The accumulation/wrong processing of the viral RNA must have led to the endothelial cell damage resulting in aHUS. This would be a new — "RNA-induced" — mechanism of aHUS.

Keywords aHUS · COVID-19 · RNA exosome · *EXOSC3* mutation

Introduction

We present two infants who developed atypical hemolytic uremic syndrome (aHUS) triggered by severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) infection. There is increasing evidence that severe coronavirus disease (COVID-19) is associated with microvascular injury like thrombotic microangiopathy and that complement activation plays a central role in the pathogenesis of severe COVID-19 — two key points of aHUS pathology [1–3].

Most aHUS cases in infants and children are due to genetic disorders of the complement system and are often triggered by viral infection or vaccinations. Our two patients presented with a very similar course of COVID-19–induced aHUS. Extensive work-up showed no complement dysfunction but the same mutation in the *EXOSC3* gene, responsible for pontocerebellar hypoplasia type 1 (PCH1b). PCH1b is a very rare autosomal recessive, neurodegenerative disorder characterized by severe, progressive neurologic impairment, neurogenic muscle atrophy, poor feeding, and characteristic findings on brain imaging [4]. To date, neither kidney involvement nor aHUS-episodes have been described in individuals with PCH1b.

First case

A 4-month-old boy of Bulgarian Roma origin with history of prematurity (26 weeks of gestation) and known neurological abnormalities since birth (microcephaly, joint contractures, axial hypotonia) presented with febrile SARS-CoV2 infection and mild respiratory symptoms 4 weeks after discharge

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from neonatology. On day 4 of hospitalization, his condition worsened. Subsequently, he developed typical signs of HUS including hemolysis, thrombocytopenia, and progressive kidney failure.

The child was admitted to the pediatric intensive care unit on day 8 with a full picture of aHUS: high LDH (3159 U/l), creatinine rising to 2.53 mg/dL, anemia (hemoglobin 8.5 g/dl), schistocytes in peripheral blood smear and thrombocytopenia (Table 1). Kidney ultrasound revealed normal-sized but echogenic kidneys. A Tenckhoff catheter was placed and peritoneal dialysis started. Complement C3c and C3d values were in the normal range, but due to high clinical suspicion for aHUS (young infant, HUS triggered by viral infection), empirical treatment with eculizumab (monoclonal antibody binding C5, preventing terminal complement complex C5b-9 formation) was initiated the same day [5].

In response to severe arterial hypertension, aggressive treatment with lisinopril, amlodipine, and clonidine was initiated. Ventilatory support was required during the first week of dialysis and the patient was treated with antibiotics (piperacillin-tazobactam). Subsequently, kidney function recovered and dialysis could be reduced after 3 weeks then discontinued after 4 weeks. Given the infant's neurological abnormalities (no gaze fixation, muscular hypotonia, microcephaly, swallowing difficulties), a brain MRI was performed and showed global brain atrophy. An ophthalmology examination revealed central visual impairment.

The boy was discharged after 6 weeks of hospitalization with nearly normal kidney function but persisting arterial hypertension still requiring a triple antihypertensive therapy (amlodipine, enalapril and atenolol). He showed severe muscular hypotonia and was entirely tube fed.

Five months after discharge, the patient still suffered from hypertension (105/62 mmHg under enalapril and amlodipine) and persisting proteinuria (albumin/creatinine ratio in urine: 295 mg/g). The creatinine was in the upper normal range for age with 0.36 mg/dl. The complement evaluation during follow-up remained normal.

Second case

A 4.5-month-old boy of Romanian Roma origin was admitted to our emergency department with pyrexia, diarrhea, and reduced drinking. SARS-CoV-2-PCR testing was positive; however, an initial blood cell count, infection markers, lumbar punction, and chest radiography were unremarkable. Abdomen and brain ultrasound were inconspicuous on admission. Initial treatment consisted of fluid resuscitation and antipyretic treatment. As the boy showed strabismus, no gaze fixation and dystonia/overextension, we performed a brain MRI. Apart from a large cisterna magna, it was unremarkable.

On day 4 of hospitalization, we observed anemia, thrombocytopenia, rising LDH, schistocytes on peripheral blood smear (Table 1) and echogenic kidneys on ultrasound. Diuresis, blood pressure, and complement C3c and C3d values were still normal, but given the clinical suspicion of aHUS, we started an empirical treatment with eculizumab the same day [5]. Despite this treatment the child's condition worsened. He developed acute kidney injury with anuria, arterial hypertension, rise of creatinine, and swollen, hyperechogenic kidneys with reduced perfusion. A Tenckhoff catheter was placed on day 8 and peritoneal dialysis initiated. The patient then suffered from severe arterial hypertension which required triple therapy with continuous urapidil, clonidine, and nifedipine infusion to achieve a moderate pressure reduction. Under continuous peritoneal dialysis, the antihypertensive treatment could be slowly reduced and switched to oral clonidine and amlodipine.

Table 1 Relevant blood values and treatments of Case 1 and Case 2

	Patient 1					Patient 2					
Day of hospitalization	1	8	16	36	46	1	4	8	11	23	30
Creatinine (mg/dl) normal < 0.39	0.15	2.53	2.17	0.72	0.53	0.35	0.47	3.87	4.07	0.52	0.29
LDH (IU/ml) normal < 295	/	3159	751	321	240	391	1111	3933	2390	438	359
Hemoglobin (g/dl) normal 9.7–13.4	10.8	8.5	9.2	8.6	9.2	10.3	9.7	5.3 *	7.6	10.0	9.4
Thrombocytes (10^9 cells/l) normal 240–550	288	59	239	649	688	320	58	126	90	510	477
Leucocytes (10^9 cells/l) normal 6.0–17.5	6.5	17.1	9.5	15.2	16.0	5.8	6.1	26.8	12.9	7.0	9.0
Eculizumab administration 300 mg		X	X	X			X		X		X
Peritoneal dialysis		Start		Stop				Start		Stop	

*Transfusion of red blood cells

On day 13 of hospitalization, diuresis recurred and dialysis was gradually reduced, then stopped on day 23. The antihypertensive treatment was also decreased and stopped. On day 30, the Tenckhoff catheter was removed. As feeding became increasingly difficult, the child was discharged almost entirely tube-fed.

Five months after discharge, the patient still suffered from arterial hypertension (110/58 mmHg under enalapril) and mild persisting proteinuria (albumin/creatinine ratio in urine: 50 mg/g). Creatinine was normal (< 0.2 mg/dl). Complement evaluation during follow-up remained normal.

For both cases a deficiency in cobalamin C metabolism, sometimes responsible for aHUS with neurological deterioration, was excluded by normal homocysteine and vitamin B12 levels [6]. Typical STEC-HUS was eliminated by negative Shigatoxin PCR in stool. Congenital thrombotic thrombocytopenic purpura was ruled out by normal ADAMTS-13 values.

Complement sC5b-9 was slightly above the normal range in both cases (456 ng/ml in case 1 and 311 ng/ml in case 2, normal value 58–239 ng/ml) as it is often seen in critically ill patients; in complement-mediated aHUS, we would have expected higher levels. Further complement functional studies (complement B, I, D, H, complement activity and anti-factor H antibodies) showed unremarkable results in both infants. The next generation sequencing (NGS) panel for aHUS revealed normal results in both patients (genes covered: *ADAMTS13*, *C3*, *CD46*, *CFB*, *CFH*, *CFHR1*, *CFHR2*, *CFHR3*, *CFHR4*, *CFHR5*, *CFI*, *DGKE*, *MMACHC*, *THBD*). Since we did not have the impression that eculizumab affected the course of the disease, we ended it even before receiving the normal genetic results.

Given the similar pattern of the disease (neurological impairment, severe course of COVID-19 complicated by aHUS, Roma background), we suspected an underlying inborn disease responsible for the neurological abnormalities and probably predisposing for aHUS development. Therefore, whole exome sequencing (WES) of both patients was performed and compared.

Both had unrelated parents. Astonishingly, WES showed exactly the same mutation in the *EXOSC3* gene, responsible for pontocerebellar hypoplasia type 1b (PCH1b). The discovered homozygous mutation c.92G > C p.(Gly31Ala) in the *EXOSC3* gene is a known pathogenic founder variant in the Roma population with a carrier frequency of 4% in the (Czech) Roma population [4, 7]. PCH1b is a rare, neurodegenerative disease characterized by progressive atrophy of the pons/cerebellum. Clinical signs include muscle weakness, progressive feeding problems, microcephaly, developmental delay, strabismus, and absent gaze fixation. In patients with p.(Gly31Ala)-mutation, life expectancy is normally < 2 years [8, 9].

Discussion

Atypical HUS is a rare thrombotic microangiopathy that accounts for about 5–10% of all HUS cases. Most aHUS cases are due to genetic disorders in the complement system leading to episodes of uncontrolled activation of the alternative complement system.

In our cases, the infants developed a severe disease with microthrombotic complications around 5 days after onset of COVID-19. Genetic disorders in the complement system were ruled out by an aHUS NGS panel.

Initially, we suggested that SARS-CoV-2 might be directly responsible for the development of thrombotic microangiopathy in our patients by inducing an overstimulation of the complement system. But complement functional studies in both patients showed no uncontrolled activation of the complement system; this strongly argues against the hypothesis of COVID19 complement-induced aHUS. In addition, if severe Covid-19 led to thrombotic microangiopathy in kidneys, we would have expected more related cases about COVID-19–associated aHUS in the setting of the pandemic [10, 11].

Whole exome sequencing of both infants revealed the same EXOSC3 mutation. The *EXOSC3* gene encodes a structural cap subunit of the RNA exosome. The RNA exosome is a multiprotein ribonuclease complex crucial for processing and degradation (quality control) of nuclear and cytoplasmatic RNA. The RNA exosome also plays a role in the decay of viral RNA [12]. There are known mutations in different subunits of the RNA exosome, all leading to distinct diseases, involving various target tissues. How dysfunction in the RNA exosome gives rise to tissue-specific disease is not yet clear. Exosome subunits might be required at different levels in different tissues and tissue-specific exosome cofactors might play a role. Thus, mutations in one subunit could affect one tissue more than another [8].

We presume that aHUS in our two patients is not due to complement-mediated thrombotic microangiopathy but rather due to defective viral RNA processing in the cells, leading to cell damage and consequently to thrombotic microangiopathy.

We suspect that the SARS-CoV-2 infection in our patients with dysfunctional RNA exosome caused an accumulation of viral RNA or a wrong processing of the viral RNA in the cell, which led to cell damage resulting in thrombotic microangiopathy and aHUS.

This would be the first description of a new — "RNA-induced" — mechanism for aHUS. Why SARS-CoV-2 infection in the presence of the defective RNA exosome primarily affected the endothelial cells of the kidneys remains unclear but might be due to tissue-specific

function of the RNA exosome and its cofactors. There is still much to be learned about the RNA exosome and deeper understanding might reveal the potential of new therapeutic strategies.

Abbreviations ADAMTS 13: A disintegrin and metalloproteinase with thrombospondin type 1 motif 13; aHUS: Atypical hemolytic uremic syndrome; COVID-19: Coronavirus disease 2019; ECG: Electrocardiogram; EEG: Electroencephalogram; EHEC: Enterohemorrhagic Escherichia Coli; EXOSC3: Exosome component 3; LDH: Lactate dehydrogenase; MRI: Magnetic resonance imaging; NGS: Next generation sequencing; TMA: Thrombotic microangiopathy; PCH 1b: Pontocerebellar hypoplasia type 1b; PICU: Pediatric intensive care unit; RNA: Ribonucleic acid; SARS-CoV: Severe acute respiratory syndrome coronavirus; STEC-HUS: Shiga Toxin producing Escherichia Coli hemolytic uremic syndrome; TTP: Thrombotic thrombocytopenic Purpura; VEP: Visual evoked potential; WES: Whole exome sequencing

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Author contribution Dr. Chantal Van Quekelberghe participated in the clinical care of the two patients, conceptualized the manuscript and the clinical implications of the case, drafted the initial manuscript, and reviewed and revised the manuscript. Dr. Matthias Hansen participated in the clinical care of the two patients, conceptualized the manuscript and the clinical implications of the case, and reviewed and revised the manuscript. Drs. Kay Latta and Steffen Kunzmann participated in the clinical care of the two patients, and critically reviewed and revised the manuscript for important intellectual content. Dr. Maik Grohmann was responsible for the genetic work-up of both patients, and reviewed and revised the manuscript for important intellectual content. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Declarations

Conflict of interest No funding was received to assist with the preparation of this manuscript. The authors have no competing interests to declare that are relevant to the content of this article.

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