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Application of combined hemadsorption with eculizumab as rescue treatment of a pediatric patient with multiple organ failure related to severe hemolytic uremic syndrome

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Abstract

Many different extracorporeal blood purification techniques have been proposed in critically ill adult patients with sepsis and sepsis-like syndromes. In this context, hemoperfusion devices such as CytoSorb have been recently approved for extracorporeal cytokine removal. In the neonatal and pediatric setting however, the application of this method brings with it various challenges including profound technical difficulties with data for its application in critically ill pediatric patients remaining sparse. We present a case of a 2-year-old female patient affected by severe Shiga toxin-producing Escherichia coli-hemolytic uremic syndrome (STEC-HUS) admitted to our Intensive Care Unit (ICU) with anuria, hemodynamic instability and severe neurological deterioration. By using a combined "rescue" therapy regimen with hemodiafiltration, hemadsorption (CytoSorb), plasmapheresis (PEX) and Eculizumab, the patient could be successfully stabilized, accompanied by a control of the hyperinflammatory response and an improvement in the neurological condition, finally leading to recovery.

In pediatric patient extracorporeal blood purification techniques might potentially represent a promising adjuvant therapeutic option for the complications related to hemolytic uremic syndrome and hyperinflammation, but further studies are needed.

Keywords: Hemolytic Uremic Syndrome, Sepsis, Cytokine Storm, CRRT, Hemoadsorption, CytoSorb, Eculizumab.

Introduction

In pediatrics, hemorrhagic gastroenteritis caused by Escherichia Coli O157:H7 producing Shiga-like toxin or verocytotoxin (STEC/VTEC) can lead to Hemolytic Uremic Syndrome (HUS) and sepsis, frequently resulting in multiple organ failure (MOF) and death [1-2-3].

HUS is a serious condition that affects the blood and blood vessels, resulting in the destruction of platelets, anemia and renal failure due to damage to the microcirculatory system of the kidneys. Other organs, such as the brain or heart, may also be affected. However, kidneys seem to be the most affected and therefore HUS is the most common cause of acute renal failure in children [4]. As STEC-HUS is characterized by a profound underlying hyperinflammatory response, elimination of excess levels of those mediators (e.g. cytokines) would be desirable. In recent years, several different extracorporeal blood purification techniques have been proposed for the treatment of critically ill adult patients with sepsis and sepsis-like syndromes. In this context,

CytoSorb has been recently approved for extracorporeal cytokine removal. In the neonatal and pediatric setting however, the application of this method brings with it various challenges including profound technical difficulties and data for its application in critically ill pediatric patients remain sparse.

We herein report the case of a 2-year-old female patient affected by STEC-HUS and concomitant anuria, hemodynamic instability and severe neurological deterioration, who could be successfully stabilized using a combined "rescue" therapy regimen including hemodiafiltration, hemadsorption (CytoSorb), plasmapheresis (PEX) and Eculizumab.

Case Presentation

A 2-year-old patient (female, 10 kg) was admitted to the infectious diseases ward due to bloody diarrhea according to the regional HUS protocol. Subsequent stool sample analysis for verocytotoxin-producing Escherichia coli (VTEC) proved positive. Over the following 48 hours, her clinical condition deteriorated rapidly including development of renal and neurological impairment, followed by transfer of the patient to the Pediatric Intensive Care Unit (PICU) and start of continuous renal replacement therapy (CRRT). Preliminary diagnosis was STEC-HUS along with hemodynamic instability (heart rate 170 bpm, mean arterial pressure<50 mmHg), severe neurological deterioration (Glasgow Coma Scale Score 6/15) and a Pediatric Logistic Organ Dysfunction-2 (PELOD2) score of 19 [5]. The patient was intubated and mechanically ventilated. She was monitored, and central venous and arterial catheters were inserted. At this time, laboratory data were as follows: leucocytes 23,000/µl, platelets 14,000/µl, hemoglobin 8.4 g/dl, C-Reactive Protein (CRP) 70.3 ng/l, procalcitonin (PCT) 81.6 ng/ml, lipase 666 U/L, amylase 269.6 U/L, ammonia 70 µg/dl, lactate dehydrogenase (LDH) 7347 mU/ml, myoglobin 209363 ng/ml, creatinine phosphokinase (CPK) 396000 mU/ml, and creatinine 3.07 mg/dl. Rescue continuous veno-venous hemodiafiltration (CVVHDF) treatment was initiated due to severe hyperlactatemia (lactate: 14.5mmol/L). The gradual onset of hemolytic crisis and contextual hyperkalemia (9.9 mmol/L) caused an arrhythmia resulting in two episodes of cardiocirculatory arrest (total 43 minutes), from which she was able to be converted back to normal sinus rhythm by cardiopulmonary resuscitation and appropriate drug administration. Additionally, high-dose epinephrine (0.2 µg/kg/min) and norepinephrine (0.27 µg/kg/min) as well as fluid therapy were started. CVVHDF (Prismaflex; Gambro, ST 20 Filter) led to normalization of the hyperkalemia, heart rate, and metabolic acidosis. On the second day of her PICU stay she showed signs of increasing rhabdomyolysis (myoglobin …, creatine kinase …) and progressive multiple organ failure (acute renal failure, MAP<50 mmHg, thrombocytopenia, hepatobiliary failure). Furthermore, a brain magnetic resonance imaging (MRI) showed large cerebellar involvement (Figure 1). For this severe case of STEC-HUS, the decision was made to administer one IV dose of Eculizumab, a monoclonal antibody against terminal complement complex, [6,7] and after a transient 12 hour CRRT discontinuation, a CytoSorb® adsorber was added to the CRRT circuit in post-dialyzer position for a total of three treatment sessions of 18 hours each separated from one another by 24-hour pause intervals (blood priming: 380 ml; blood flow rate: 200 ml/min). Within 24 hours of CytoSorb® treatment, her hemodynamic status improved significantly (MAP 80 mmHg) and vasopressors could be gradually decreased (Table 1). This was paralleled by a reduction in inflammatory parameters (CRP, PCT, leucocytes 8.220/µl), a normalization in ammonia levels and an increase in platelets (131.000/µl). Other parameters such as LDH (840 mU/ml), myoglobin (383 ng/ml), CPK (1465 mU/ml), lipase (412 U/L) and amylase (12.7 U/L) also improved. Urine output was 200 ml/24 h (Table 1). Upon discontinuation of CytoSorb, a second infusion of Eculizumab was administered [8]. As electroneurography and electromyography showed an inflammatory polyneuropathy, one session of plasma exchange was started. Repeat brain MRI and electroencephalography showed a complete recovery (Figure 1) on the 15th day of admission. Respiratory weaning was started on day 6. She was extubated on day 10 and non- invasive assisted ventilation was continued for 3 days without the necessity for tracheotomy. The patient was transferred to the nephrology ward on day 13 with a PELOD2 score of 7 and finally discharged to rehabilitation? on day 20 with no neurological sequelae and normal renal function. The patient underwent 60 days of rehabilitation until she was able to walk unaided again.

To our knowledge, this is the first report describing the use of extracorporeal CytoSorb hemoadsorption therapy combined with hemodiafiltration, plasmapheresis and Eculizumab in a pediatric patient with hemolytic uremic syndrome and multiple organ failure. Treatment was associated with clear hemodynamic stabilization and a concomitant reduction in vasopressor doses, while hyperinflammation could be well controlled, and profound progression of neurological deterioration presumably prevented. CytoSorb hemoadsorption was technically feasible and well-tolerated with no device related adverse events occurring in this patient.

It is therefore proposed that the use of CytoSorb could represent a new adjuvant therapeutic approach in the treatment of HUS related septic shock in the pediatric context, particularly in conjunction with the application of monoclonal antibodies as this combination might be able to interrupt the pathologic process via different targets. CytoSorb treatment was associated with a reversal in the patient's vasoplegic septic shock state, most probably induced by excess inflammatory mediators, as evidenced by rapid hemodynamic stabilization and reduction in vasopressor drugs. Similar conclusions have already been drawn from various other publications [9,10]. Of note, our case is somewhat unique in that we applied a complex combined therapeutic approach using Eculizumab and different extracorporeal blood purification techniques (i.e. CVVHDF, CytoSorb and plasma exchange), which has not been used before, particularly in the pediatric setting. Scheibenpflug [11] and colleagues treated a pediatric patient of

the same age with STEC-HUS with CRRT, however intestinal necrosis occurred due to persistant hemorrhagic colitis with perforation. In this case, after the onset of liver failure, a total of 5 cycles of extracorporeal blood purification were performed. Due to a rebound in cholestasis and hyperammonemia markers following cessation of extracorporeal blood purification techniques, 4 cycles of combined CVVHDF and CytoSorb hemoadsorption were started, resulting in the preservation of liver and renal function. In contrast to our patient, this case required 3 months recovery on the PICU, most probably because of the delayed use of CytoSorb. Based on our observations in this single case, CytoSorb therapy might potentially represent a promising and important adjuvant therapeutic option to help manage the serious complications caused by hemolytic uremic syndrome and hyperinflammation in pediatric patients while further studies are obviously needed in this field.

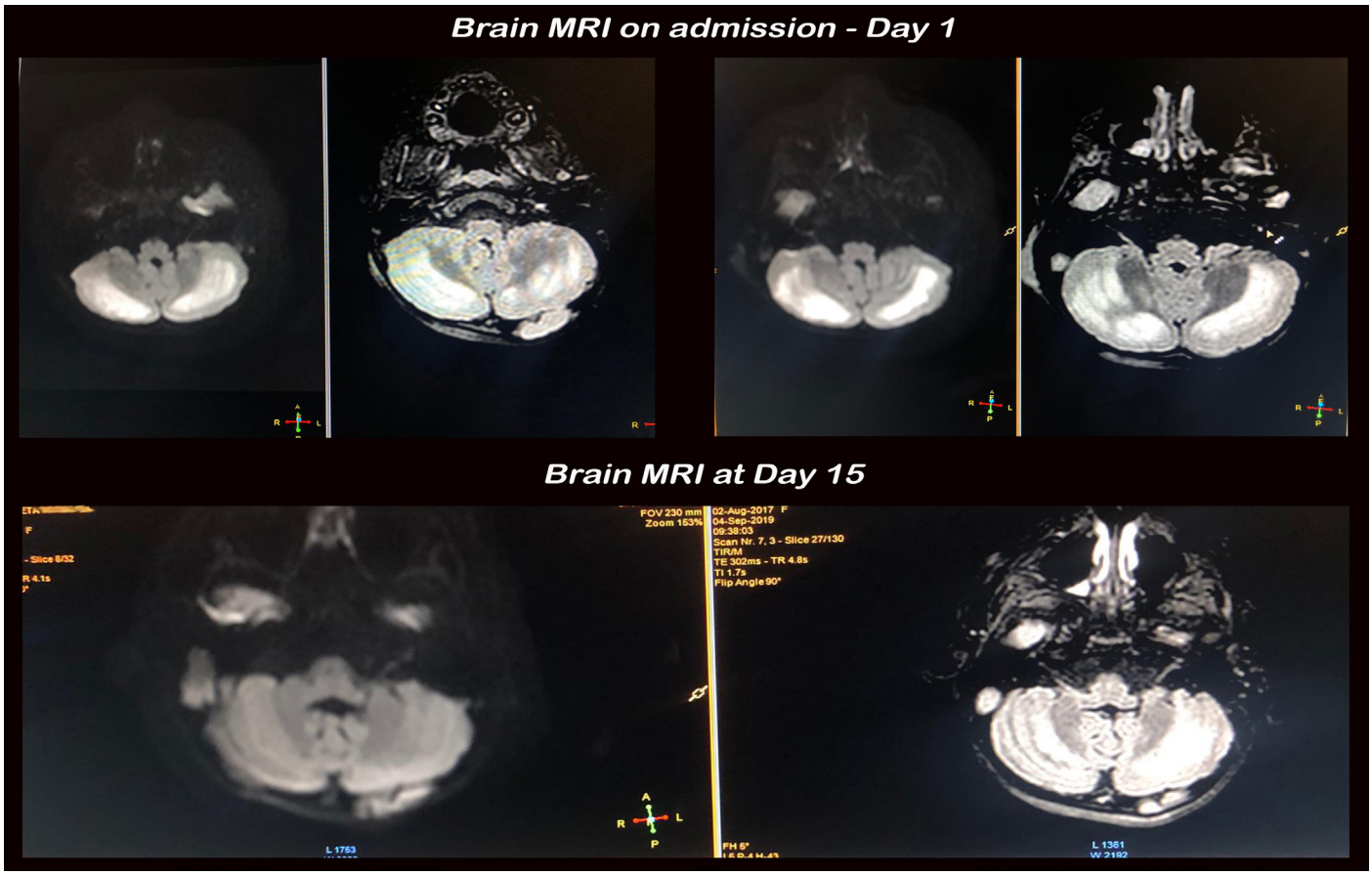

Figure 1: Brain MRI.

Table 1: Patient's data before, during and after the treatment.

PARAMETERS	ADMISSION	DYALISIS ST	BEFORE 1ST CytoSorb TREATMENT	AFTER 1ST CytoSorb TREATMENT	AFTER 2ND CytoSorb TREATMENT	After 3RD CytoSorb TREATMENT	PLASMAPHERESYS	DISCHARGE
HEMATOLOGY								
WBC	23	14.25	14.09	17.52	15.6	8.22	22.18	17
PCR	19.1	70.3	45.9	79.4	69.8	61.3	47	5.9
PCT	81.6		47.24	17.9		5.9		
HCT	23	29.53	29	25.91	27.02	29.7	33.4	30.9
HB	8.4	10.3	10.6	9.2	9.6	10.8	11.7	10.9
PLT	14	36	37	14.9	18	22	18	131
RENAL/ HEPATIC FUNCTION								
AZOTEMIA	147	4.9	30	26	26	37	97	159
CREATININE	3.07	1.47	0.42	0.36	0.35	0.41	0.93	1.06
BILIRUBIN	1.85	1.33	1.81	1.9	1.2	1.65	1.11	1.14
AMILASE	269.6	117.98	103.36		1.408	12.7		
LIPASE	499	666	222	1.222	570	412	709	955
MIOGLOBINE	970	205.712	209.363	14.587	1.245	383	295	106
LDH	5.234	7.899	7.347	3.516	2.056	1.465	840	668
CPK	81.704	396	239.48	51.377	9.041	2.401	709	273
EGA								
PH	7.24	7.45	7.46	7.46	7.48	7.44	7.35	7.4
PCO2	16	31	40	43	38	34	34	36
PO2	579	233	205	171	274	243	114	240
LATT	14.5	0.9	1.2	1	1.3	3.5	1.1	1
K	9.9	3.5	3.3	3.4	4	3.6	3.4	3.2
BE	18.3	1.8	4.6	6.1	4.8	1.1	6	2
AMMONIO	70	46	66	56				
HEMODYNAMICS								
MAP	50	76.5	78	85.5	78.5	96	95	87.5
PAD	30	54	63	68	58	107	115	125
PAS	70	99	93	103	99	85	75	50
FC	210	157	144	159	119	118	79	130
AMINES								
EPINEPHRINE	0.2	0	0	0	0	0	0	0
NOREPINEPHRINE	0.27	0.2	0.2	0	0	0	0	0
COAUGULATION								
INR	3.77	0.98	0.98	1.06	1.36	1.35	1.02	1.09
PTT	1.64	1	0.94	1.16	1.59	1.51	1.11	0.87
FIB	226	397	276	493	441	282	141	87
DIDIM	9.98	3.52	9.92	4.57	2.995	13.86	8.79	4.05
ATIII	70	85	90	113	110	105	83	89
DIURESIS h24	0	0	0	0	0	10	50	200

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