ORIGINAL SCIENTIFIC ARTICLE

TREATMENT OPTIONS IN PATIENTS SUFFERING FROM HEMOLYTIC-UREMIC SYNDROME: THE SERBIAN MILITARY MEDICAL ACADEMY EXPERIENCE

Jelena Tadic, Mirjana Mijuskovic, Marijana Petrovic, Katarina Obrencevic, Brankica Terzic, Violeta Rabrenovic, Neven Vavic and Đoko Maksic

Military Medical Academy, Clinic for Nephrology, Belgrade, Serbia

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Corresponding author:

Jelena Velimir Tadic

Military Medical Academy, Clinic for Nephrology, Belgrade, Serbia

E-mail: j.tadic2010@gmail.com

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ABSTRACT

Hemolytic-Uremic Syndrome (HUS) is a clinical syndrome with a triad of non-immune Microangiopathic Hemolytic Anemia (MAHA), thrombocytopenia and renal failure. Together with the Thrombotic Thrombocytopenic Purpura (TTP), it belongs to a group of diseases characterized as the Thrombotic Microangiopathy (TMA), which represents a microvascular occlusive disorder with the formation of a predominantly thrombocytic thrombus in the renal and/or systemic circulation. In the period starting from 2001 to 2017, 14 patients with a HUS were diagnosed at the Clinic for Nephrology (unfortunately ADAMTS 13 could not have been done due to technical reasons). In a retrospective clinical laboratory analysis and monitoring, we obtained the following results. Out of 14 patients, 10 were female (or 71.43%) and 4 were male (28.57%), the youngest patient was aged 17 and the oldest one 78, the average age of our patients was 55.33 years, the annual number of patients with the diagnosis of HUS was 0.93 patients per year, or 0.00116 in relation to the total number of patients treated. After monitoring the patients individually for the period ranging from 1 to 14 years, a stable remission was achieved in 5 patients, while a chronic renal insufficiency occurred in 3 patients. In two of our patients, a percutaneous kidney biopsy was performed with pathohistological findings described in references. Having done this retrospective analysis, we can conclude that the survival and complications of this rare, but serious disease correspond to the available world data.

Keywords: *Hemolytic-uremic syndrome, atypical hemolytic-uremic syndrome, C3, corticosteroids, plasmapheresi.*

INTRODUCTION

Hemolytic-Uremic Syndrome (HUS) is a clinical syndrome with a triad of non-immune Microangiopathic Hemolytic Anemia (MAHA), thrombocytopenia and renal failure. Together with the Thrombotic Thrombocytopenic Purpura (TTP), it belongs to a group of diseases characterized as the Thrombotic Microangiopathy (TMA), which represents a microvascular occlusive disorder with the formation of a predominantly thrombocytic thrombus in the renal and/or systemic circulation. According to the International Society on Thrombosis and Hemostasis (ISTH) Guidance published in 2005, this term is used for all diseases or conditions with the hemolytic anemia (with schistocyte formation) and consumptive thrombocytopenia (1). The TMA was first mentioned in references named as the Moschcowitz syndrome after Dr Eli Moschcowitz, who first described such a case at a hospital in New York in 1925. The term HUS dates back to 1955, when Dr Conrad von Gasser et al. published a case describing five children with the hemolytic anemia, thrombocytopenia and dominant acute renal insufficiency (2). Karmali first established the relationship between the HUS and E. coli infection in 1985 (3, 4). Nowadays, many years later, the HUS is still defined as a clinical triad, but with significant advances in clarifying the etiology and pathophysiology of this relatively rare disease. D+ HUS, a typical type of HUS or Stx-HUS etiopathogenesis occurs about a week after the episode of bloody diarrhea caused by the enterohemorrhagic E. coli infection, most commonly by serotype 0157: H7 (70%). Other E. coli serotypes (O111: H8, O103: H2, O121, O145, O26 and O113), Shygella dysenteriae serotype 1 and rarely other enteral bacteria can also be the cause of infection (5-8) D−HUS, an atypical type of HUS or non-Stx-HUS etiopathogenesis accounts for only 5 to 10% of all cases. In 1975, Kaplan et al. observed for the very first time that there were two types of the atypical HUS, sporadic and familial, which were characterized by a reduced level of serum C3 protein, the central component of the human complement system. Genetic studies have shown that mutations in the genes encoding the complement regulatory proteins predispose the development of this type of disease. The following factors are important for the development of the disease: factor H, factor I and Membrane Cofactor Protein (MCP). So far, more than 50 mutations have been described for the Complement Factor H (CFH), a plasma protein that inhibits the activation of the alternative complement pathway by the inactivation of C3 convertase. The familial type of HUS makes up for less than 3% of all HUS cases, and occurs as a consequence of a hereditary defect or a complement factor H (CFH) defect. Thompson and Winterborn were the first to describe this disease in 1981 in patients with very low levels of C3 protein in plasma and a decreased CFH level. The disease can be inherited autosomically recessively and autosomically dominantly. The recessive inheritance is combined with a low level of CFH, which can range from 10 to 50% of normal concentration, a reduced C3 complement component, and the development of HUS in early childhood. The prognosis is poor with a mortality rate ranging from 60 to 70%. The autosomal dominant type of the disease is associated with a functionally abnormal CFH level, a normal C3 level, followed by a development of HUS in special conditions such as, for example, an infection or pregnancy. Moreover, there is one more type of HUS, the post-transplantation HUS (pHUS), which represents a known and serious complication that can arise after the transplantation of solid organs (kidney, heart, lung, liver, pancreas, small intestine) and hematopoietic stem cells. It is clinically manifested most commonly with the sudden onset of hemolytic anemia, thrombocytopenia and the development of renal insufficiency (15, 16).

PATIENTS AND METHODS

In the period from 2001 to 2017, 14 patients with aHUS were diagnosed at the Clinic for Nephrology (unfortunately ADAMTS 13 could not have been done due to technical reasons). The research was carried out by the means of retrospective analysis and monitoring.

RESULTS

In a retrospective clinical laboratory analysis and monitoring, we obtained the following results. Out of 14 patients, 10 were female (or 71.43%) and 4 were male (28.57%); the youngest patient was aged 17 and the oldest one 78, the average age of our patients was 55.33 years. The total number of patients treated for all diagnoses at the MMA Clinic for Nephrology from 2001 to 2016 was 12,025, with the average of 858.92 patients per year. The annual number of patients with the diagnosis of HUS was 0.93 patients per year, or 0.00116 in relation to the total number of patients treated. Out of 14 patients, 9 patients were O Rh(D) positive, and the rest were A Rh(D) positive blood group. At the time of diagnosis of HUS, the mean serum creatinine levels in these patients were 321.78 umol/l, the mean hemoglobin was 81.83 g/l, while the mean platelet count was 53.49. Hemoglobin levels were reduced in all monitored patients (100%), out of whom 28.57% had hemoglobin levels below 80 g/l at admission. Serum albumin was slightly decreased in 71.43% of the monitored patients. Only in 5 patients, the value ranged from 21-30 mmol/l, (35.17% of cases), while only one of the monitored 14 patients had indirect bilirubin levels in reference values (0.07%) (Table 1).

Table 1. The laboratory parameters in our patients

	1	2	3	4	5	6	7	8	9	10	11	12	13	14
SE	>100	7	>100	>100	60	85	71	88	>100	>100	>100	>100	>100	>100
CRP	1.2	1.7	1.15	24.6	1.8	48.7	188	24.8	1.5	45.8	1.52	1.8	5.86	128
Leu	9.8	9.11	10.2	5.07	8.9	22	7.5	18.4	9.9	16	11	11.1	9.9	12.8
Eri	3.32	2.98	3.6	2.72	3.12	2.24	2.52	2.59	2.9	2.29	2.99	2.68	2.88	2.7
Hgb	98	92	96	92.5	87	61	81.9	81	88	56.4	82.4	82.4	76	71
Tro	8	69	58	62.8	67	17	87	88	67	9.9	28	89	91.1	7
sCre	286	159	229	190	547	248	884	128	289	150	821	115	458	286
Alb	33	34	34	31	28	28	29	34	31	25	31	35	25	21
Bil/ dir	128/12	108/12	89/17	91/17	11	20/6	28/4	48/17	29/11	25/7	25/8	48/12	27/8	49/9
Coom.t	neg	neg	neg	neg	neg	neg	neg	neg	neg	neg	neg	neg	neg	neg
LDH	8462	8244	2548	6041	884	1151	2086	1154	2281	1868	461	984	1568	1218
AST	57	96	49	59	24	42	111	19	88	56	11	188	78	88
ALT	26	80	81	26	27	24	56	27	48	21	82	78	69	68
HPT	0.4	0.01	0.8	0.02	0.8	0.06	0.08	0.07	0.4	0.06	0.01	0.9	0.09	0.08
Imun	-	-	-	-	-	-	-	-	-	-	-	-	-	+
Tu	-	-	-	-	-	-	-	-	-	+	+/-	-	-	+/-
Frag	rare	rare	14%	1%	rare	rare	12-14%	much	17%	rare	rare	1-5%	5%	5%
24h Pr urine	2.26 gr	b.o.	1.3 gr	550 mg	1.8 gr	7.53 gr	330 mg	547 mg	2.8 gr	6.8 gr	13.2 gr	342 mg	7.9 gr	8.2 gr

**Note: pink colored fields indicate a pathological finding*

Serum haptoglobin levels were significantly decreased in all patients. Moreover, in 64.28% of patients the levels were barely measurable (0.00 ...). Lactate dehydrogenase was significantly increased in all patients, i.e. in 11 patients the value was higher than 1000 (78.57%), and in 3 patients levels were increased, but lower than 1000. The Coombs test was negative in all patients. C3 and C4 (17) levels were not measured in all patients (due to the lack of reagents, although they were initially required) and were not taken into account in monitoring our patients. In one patient (7.14% of total patients monitored) we observed significantly elevated tumor markers (CEA, CA 19-9, NSE), in two patients (14.28% of total patients monitored) we observed an elevated non-specific tumor marker (CEA) while in one patient, (7.14% of total patients monitored) we observed increased levels of immunological markers. Only in one patient (7.14%) the 24h proteinuria (Biuret method) was in reference values, in 5 patients (35.17%) the 24h proteinuria was nephrotic (or greater than 3.0gr/24h), while in 4 patients (28.57%) the 24h proteinuria was less than 1.0gr/24h (at admission the possibility of prior administration of SSP or sAlb was excluded, with unknown data concerning the 24h proteinuria, i.e. the presence of previously diagnosed glomerulopathy was excluded).

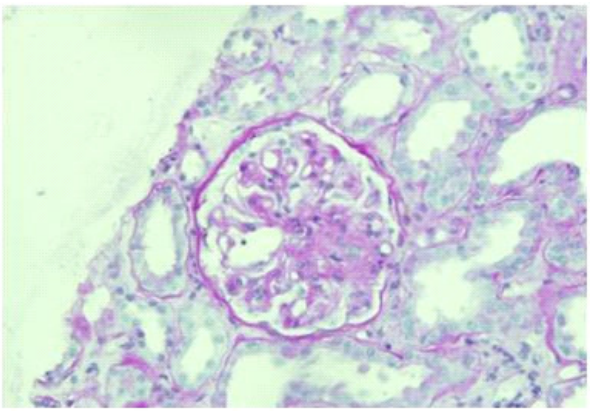
13 patients (86.6%) were treated by the SSP and therapeutic plasma exchange – plasmapheresis and 11 patients (78.57%) were treated by the therapeutic plasma exchange (during plasma treatment, the number of blood platelets, creatinine concentration and serum lactate dehydrogenase is determined daily, 26.) and corticosteroids, while in 7 patients (50%) the treatment was performed together with intermittent hemodialysis (HD) procedures as a supportive therapy. The average number of hemodialysis procedures performed in these patients was 8 (ranging from 3 to 18 HD procedures/patient, Table 2).

Table 2.

	1	2	3	4	5	6	7	8	9	10	11	12	13	14
TPI	20	13	11	4	0	6	2	88	23	2	31	18	5	4

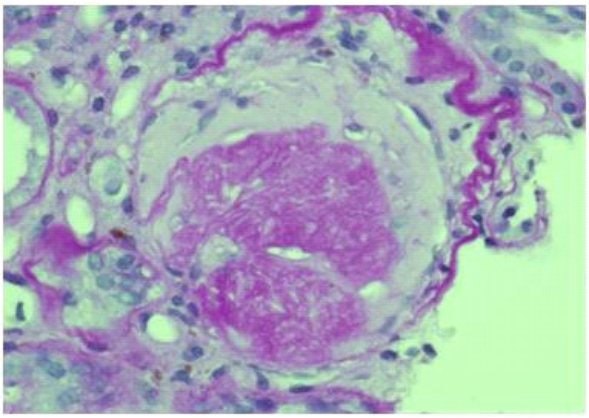
Three patients were treated by the TPI, a multi apheresis procedure at the MMA Institute of Blood Transfusion and Hemobiology, with the great help of our colleagues at the Institute. The decision to implement the TPI at the Institute of Blood Transfusion and Hemobiology was made due to a weaker response to the volume exchange performed at the Department for Hemodialysis, according to standard protocol. The efficacy was being monitored indirectly by tracking the increase in the platelet count, as well as the decrease in indirect bilirubin and LDH. The normalization of the tracked hematological parameters was achieved in the average period of 29.8 +/- 2 days. In one patient, after a consultation with a Hematologist, due to the refractory disease response to the applied therapeutic protocols combined with corticosteroids, Cyclophosphamide was administered (iv infusions every 15 days according to the creatinine clearance). In one female patient, due to the combined clinical picture of the TTP/HUS, we administered Vincristine together with corticosteroid therapy. In one female patient, due to the refractory disease response to the therapeutic plasma exchange, together with corticosteroids (88 TPI) and occasional multi apheresis procedures, Rituximab was administered at a dose of 375 mg/week according to standard protocol. Regardless of the procedures applied, there were no complications due to sepsis as a consequence of the temporary central venous catheter in any of our patients. So far, in the Republic of Serbia, Eculizumab has not been given for this diagnosis (18- 20). After monitoring the patients individually for a period ranging from 1 to 14 years, a stable remission was achieved in 5 patients (recovery without relapse, without diagnosing the SBVT and/or neoplastic processes of any etiology in the meanwhile), while a chronic renal insufficiency occurred in 3 patients (two patients with the MDRD above 40 ml/min/1.73 m2, and one patient with the MDRD 11.3 m/min/1.73 m2). A lethal outcome occurred in 6 out of 14 patients (42.86%). In 2 out of 6 patients, the fatal outcome occurred 96 hours after the admission to our Clinic, which could neither be associated with the hematologic parameters monitored (prevalently with thrombocytopenia), the time of hemodialysis commencement, the number of hemodialysis performed, nor with the number of therapeutic plasma exchanges done, but with the clinical findings of the life-threatening condition of the afore-mentioned patients at the admission. These patients were in deep somnolence/sopor, the cause of death was assumed to be the TMA, but of an unknown origin, due to the fact that the consent from their relatives for a clinical autopsy could not be obtained. In one female patient, despite our best efforts and the implementation of all treatment options (hemodialysis, 88 TPI, Rituximab), a lethal outcome occurred after 11 months, while in 3 out of those 6 patients, lethal outcomes occurred within a period of at least 24 months after discharge from our institution. The average life span of these patients was 74.8 years and there were no available data concerning the final diagnosis and cause of death. In two of our patients, a percutaneous kidney biopsy was performed with pathohistological findings described in references, with no complications in the post-biopsy recovery in terms of retroperitoneal bleeding and/or perirenal, i.e. intrarenal hematoma (see pictures 1 to 4, with a brief explanation with them, the pathohistological finding corresponds to the finding encountered at the HUS / TTP).

Picture 1.



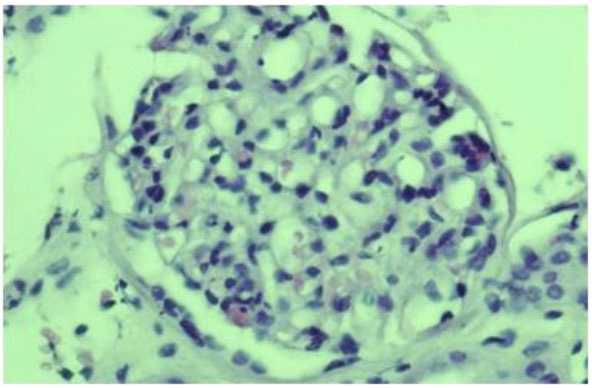
11139-15 HE 40x B.M., female,
hialini thrombus segments in the lumen
of the capillary

Picture 2.



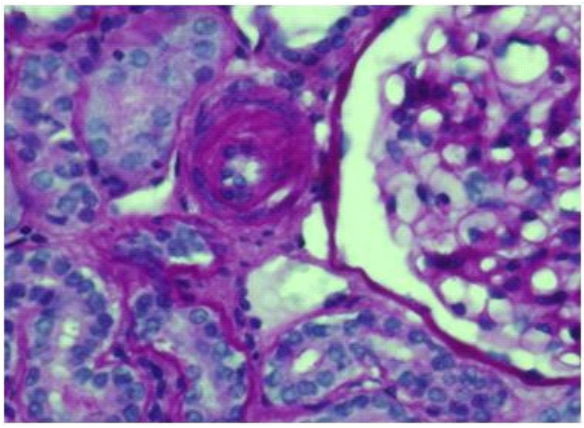
11139-15 PAS 40x B.M., female,
hyperplastic arteriolitis

Picutre 3.



8832-14 pas 40x Đ.L., female,
sclerotic glomerul in the form of vascular
obliteration

Picture 4.



8832-14 pas 20x Đ.L., female,
segmental glomerulosclerosis in the field
of ischemic lesion

DISCUSSION

In our patients, who were monitored from 2001 to 2017, thrombocytopenia, i.e. the platelet count, could not be linked to the severity of the clinical presentation of these diseases, which coincides with the available reference data (24, 25). The number of platelets at admission could not be linked to the total number of TPIs applied individually in patients. Also, only one patient had the 24h proteinuria in reference range; while 5 patients had a nephrotic 24h proteinuria, with no prior knowledge of having a glomerular disease that could be associated with the severity of the glomerular damage. Moreover, while monitoring our patients, we observed that the maintenance of nephrotic range proteinuria for more than 3 months significantly affected the occurrence of chronic renal disease and reduced survival rate of such patients. The administration of corticosteroid therapy reduced chronic complications and significantly reduced the period of normalization of characteristic hematological parameters in these patients (an average of 29.8 days), which correlated with the data available in references (data from multicenter, non-randomized studies, with a small number of patients treated with *Eculizumab,* cumulative observation period of 95 months, 3 of the 10 patients experienced relapse within 6 weeks of discontinuation, but then immediately resumed treatment and completely recovered, but only 10 patients were observed) (21-24). Determining the ADAMTS 13 would significantly help us assess the course of the disease and expected survival rate of these patients, as well as assess the possible necessity of applying a "more aggressive" treatment with monoclonal antibodies, currently unavailable in our institution. The possibility of opening a reference center for treating these patients in institutions that can provide a multidisciplinary approach and the TPI, a multi apheresis procedure, would be particularly encouraging. Our results in treating this serious, life-threatening disease (25-27), concerning the percentage of survival and the acute and/or chronic complications (infections, the onset and/or aggravation of renal insufficiency) correspond with the data available in references.

CONCLUSION

Timely diagnosis (the Hemolytic-Uremic Syndrome), the initiation of therapeutic plasma exchanges, the inclusion of corticosteroids and, if necessary, hemodialysis procedures, significantly improve the survival rate of these patients. In patients admitted to our institution with the diagnosis of the TMA/HUS/TTP, most likely an atypical type, without the previous existence of an infectious and/or diarrhea syndrome, the treatment was conducted with the *Prednisone*, SSP, TPI and hemodialysis with/without therapy *(Cyclophosphamide/Vincristine/Rituximab)*. Having conducted this retrospective analysis, we can conclude that the survival rate and complications of this rare, but serious disease correspond to the available world data. Thus, we can conclude that the recognition of these patients is crucial, and so is their referral to institutions that can provide multidisciplinary treatment methods, together with sub-specialists from the Internal Disease Clinics.

Furthermore, whether this syndrome belongs to a group of diseases that Nephrologists and/or Hematologists cure stays the utter dilemma.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

All research procedures were approved by the Ethics Committee Serbian Military Medical Academy Belgrade, Serbia. The study was conducted in accordance with the ethical standards of the committee responsible for human experimentation (institutional and national) and the Helsinki Declaration of 1975, as revised in 2013. Voluntary written and informed consent was obtained from each participant prior to enrollment in the study

CONFLICT OF INTEREST

There are no conflicts of interest.

FUNDING

None.

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