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Hemolytic Uremic Syndrome: Single Centre Experience

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Introduction: Hemolytic uremic syndrome (HUS) is a clinical syndrome characterized by non-immune microangiopathic hemolytic anemia, thrombocytopenia and acute renal failure. In this study, we aimed to evaluate patients diagnosed with HUS in our clinic.

Method: Patients who were diagnosed with HUS as clinic and laboratory between August 2012 and October 2017 were included in our nephrology clinic. Biochemistry, haemogram, ANA, anti-Ds DNA, p-ANCA, c-ANCA, anti-GBM antibody, C3, C4 of patients were studied. In some cases, ADAMTS13 was studied and renal biopsy was performed. The demographic features, clinics and treatments of our cases were reviewed.

Results: A total of 18 patients were enrolled in the study, the average age of the patients was 48.3 (21-82) and 10 of the cases were female and 8 of the cases were male. Among the etiologic causes of HUS in patients; the complement factor B mutation, complement factor H polymorphism, breast cancer, herbal medicine, infections and idiopathic were detected. Primer glomerulonephritis was detected in 6 cases of renal biopsy.

Conclusion: Clinical and laboratory remission was obtained in 13 patients. End-stage renal failure developed in 3 of our patients.

Keywords: Acute kidney damage, microangiopathic hemolytic anemia, thrombocytopenia, eculizumab

Introduction

Hemolytic uremic syndrome (HUS) is a syndrome characterized by microangiopathic hemolytic anemia, thrombocytopenia and acute renal failure triad. It is defined as being Incomplete HUS, acute renal failure, thrombocytopenia or microangiopathic hemolytic anaemia (1). Traditionally, it is classified as HUS diarrhea positive HUS (D+HUS) and diarrhea negative atypical HUS (aHUS). Enterohemorrhagic E. coli (EHEC) is responsible for 90% of childhood HUS cases. The incidence was reported as 2-3 for every 100,000 children. Typical HUS, known as food-borne, appears to be one in every 100,000 people per year, while it is 6 in adults under 5 age, it is 1 in adults. Although HUS is rarely reported, it has been reported to have epidemics. It is known that these outbreaks originate from the food that is transmitted by animal feces. Recently, in Germany and 15 European countries, there is a known epidemic of food (2-5).

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Some cases of aHUS in children are associated with methyl malonic aciduria (6), invasive streptococcal pneumonia (7), which more often produces neuraminidase enzyme (5% of HUS cases in children), may develop as a result of H1N1 viral infection (8). In adults, thrombotic microangiopathy can develop as a result of HIV infection, cancer, drugs [chemotherapeutic drugs, calcineurin drugs (cyclosporine, tacrolimus), mTOR inhibitors (sirolimus, everolimus), vascular endothelial growth factor inhibitors, antiplatelet agents, oral contraceptives and other drugs, malignant hypertension, bone marrow and solid organ transplantation, systemic diseases (SLE, scleroderma, and antiphospholipid syndrome)] (9).

Materials and Method

A total of 18 patients who were diagnosed with HUS as clinic and laboratory between August 2012 and October 2017 were included in our Nephrology clinic. Coombs negative microangiopathic hemolytic anaemia, lactate dehydrogenase (LDH) and reticulocyte elevation, thrombocytopenia and acute renal failure were present in all the cases included in the study.

In patients, serum creatinine, blood urea nitrogen, electrolytes, LDH, liver enzymes, bilirubin, hemogram, reticulocyte, direct Coombs test, peripheral spread, anti-neutrophil cytoplasmic antibody, antiglomerular basement membrane antibody, antinuclear antibody, anti-double stranded DNA, complemet C3 and C4 levels were measured. In addition, viral markers were also examined. In cases of diarrhea, EHEC antigen was examined. Renal biopsies were performed in patients receiving renal biopsy. Genetic mutation was observed in three cases.

Results

A total of 18 patients were enrolled in the study, the average age of the patients was 48.3 (21-82) and 10 of the cases were female and 8 of the cases were male. Acute kidney damage, microangiopathic hemolytic anemia and thrombocytopenia were detected in all cases. Neurological findings could not be detected in any of our cases. EHEC did not produce in any of the cases with diarrhea (9 cases). There were fever in five cases, jaundice in 8 cases, and nausea-vomiting complaint in 10 cases. In all cases, there were schistocytes in the peripheral spread. Coombs test was negative in all patients, haptoglobulin levels were found to be low in the six patients examined, INR was within normal limits for all but acute cholecystitis.

Autoantibodies, anti-neutrophil cytoplasmic antibody and antiglomerular basement membrane antibody were negative in all patients, antinuclear antibody was positive in 2 cases, anti-double stranded DNA was negative. ADAMTS 13 was worked on 8 cases and was determined at normal values. The laboratory data of the patients were given in table-1.

Etiologically, in one of the cases salmonella species were derived, a case developed during the epidemic of salmonella but there was no reproduction. In one case, Escherichia coli (E. Coli) derived both in blood and urine, in one case E. Coli derived in urine and in one case E. Coli derived in blood, and in one case E. Coli derived in gaita culture. In one case, there was a story about the use of Panax herbal medicine to lose weight. In one case, there was a gemcitabine usage story for breast cancer. In three cases, the complement mutation was observed. In one case, complement factor B heterozygous mutation, complement factor H polymorphism was detected in a case with

acute cholecystitis. In the other case, no mutation was detected. The etiology of our other cases was unclear.

Treatment included plasma exchange, hemodialysis (HD), prednisolone, angiotensin receptor blockade, fluid and electrolyte support. Erythrocyte suspension replacement was necessary in 68.7% of our cases. HD and plasma exchange for 6 cases, only HD for 8 cases, only plasma exchange for 1 case, in one case only fluid electrolyte therapy and ES replacement were performed.

In our three cases, end stage renal failure (ESRD) developed. In the presence of complement factor H polymorphism, treatment with eculizumab was initiated. ESRD developed in the patient with complement factor B heterozygous mutation. The patient died before the end of mutation (at 6 months of HD program).

The renal biopsies, treatment approaches and outcomes of the patients were given in table 2. Three patients were treated with eculizumab. One of these patients was ESRD, he was in 4 months HD program. Developing complement factor H polymorphism and upon frequent attacks, the patient began treatment. After the treatment, our patient was not attacked again and there was an increase in urine volume, but HD continued. In one case HD was continued with ESRD. In another case, complete recovery was observed after treatment with eculizumab.

Discussion

HUS and thrombotic thrombocytopenic purpura are characterized primarily by endo-thelial damage followed by thrombosis, microangiopathic hemolytic anaemia, and thrombocytopenia and multiorgan failure. HUS is divided into 3 types; 1- It is associated with diarrhea and is associated with infections, is defined as D (+)

Table-1. Laboratory findings of HUS cases

Case No	Serum Creatinine (mg/dl)	Hemo-globin (gr/dl)	Thrombocyte count (mm^3)	Reticulo-cyte (%)	Lactate dehydro genase (IU)	Indirect bilirubin (mg/dl)	C3/C4	Micrototal protein (gr/gün)
1	7,9	10,4	22000	1,79	3380	N	N/N	0,9
2	3,7	10,4	12000	1,9	1045	N	Low/N	2,3
3	1,8	6,3	82000	7	1660	5,7	N/N	2,1
4	8,6	8,6	107000	2,8	752	2	Low/N	0,68
5	8,8	8,5	77000	2,8	1072	3,7	N/N	0,9
6	8,8	10	98000	1,9	704	N	N/N	1,1
7	4,3	10,9	22000	2,2	1063	N	Low/N	5,1
8	5,6	7,7	46000	4,8	1496	2,1	N/N	0,84
9	2,8	5,9	77000	2,8	3074	5	N/N	2,6
10	15	7,0	91000	13	1062	3,2	Low/N	2,4
11	4,5	8,78	77000	3,7	802	N	Low/N	4,2
12	3,3	9,0	68000	3,1	924	N	N/N	1,2
13	7,6	7,2	61000	2,6	4121	4,1	Low/N	anuric
14	104	10	28000	6	1539	N	Low/N	18
15	6,8	9,0	143000	1,8	1597	2,8	N/N	0,4
16	7,4	6,5	70000	3,8	1123	3,4	Low/N	1,8
17	6,0	11,9	35000	9	1155	N	N/N	1,2
18	4,2	7,8	30000	1,92	4147	2,28	Low/Low	2

HUS, (except HUS due to severe disseminated infection caused by streptococci), 2-complement abnormalities or atypical HUS (aHUS), which is associated with a factor ADAMTS13 deficiency at the same time, 3-HUS with no known etiology develops in systemic diseases, physiopathological conditions such as pregnancy, renal transplantation and post-drug (5). In fact, all three are the changes in the basic pathology complement system. In this system, the uncontrolled activation of the complement system results in endothelial disorders and micro vascular thrombosis. It was found in different strains, although it was generated by E.coli 0157/H7. In the E coli outbreak that

Table-2. HUS renal biopsy and treatments

Case	Etiology	Renal biopsy	Treatment	Result
1	Heterozygote CFB	Renal biopsy compatible with microangiopathic	PE (12times), 3 days 1 gr prednisolone followed by 1 mg / kg lowered, 4Ü ES replacement, HD	SDBY ex
2	Unclear	Immune Complement glomerulonephritis	Liquid and electrolyte 2Ü ES replacement valsartan 160mg 1x1	Proteinuria
3	Unclear	Not Performed	Prednisolone 30 mg/day, PE 6 times, 6Ü ES replacement	Normal
4	Unclear	Mesangialproliferative glomerulonephritis.	PE 8 sessions , HD 5 times Prednisolone 1mg/kg, Valsartan 160mg/day	Normal
5	Panax	Not performed	HD 8 sessions, 2Ü ES replacement	Normal
6	Salmonella species	Not performed	HD 5 sessions, 14 day ciprofloxacin 500mg 1x1	Normal
7	Unclear	Not performed	HD 8 sessions	Normal
8	Unclear	Not performed	HD 4seans, 2Ü ES replacement	Normal
9	E. Coli	Mesangialproliferative glomerulonephritis.	HD 8 sessions, ciprofloxacin 500 mg 2x1, valsartan 160mg 1x1, prednisolone 1mg/kg, 5Ü ES replacement	Normal
10	Unclear	Not performed	Prednisolone 1mg/kg, HD, PE 15 sessions	ESRD
11	Unclear	Not performed	HD 2 sessions, 2Ü ES replacement	Normal
12	E. Coli	Not performed	Liquid and electrolyte, 2Ü ES replacement, Ciprofloxacin 500mg 2x1	Normal
13	Acute cholecystitis CFH polymorphism	Renal biopsy compatible with microangiopathic	Metronidazole injection 3x1, Piperacillin / Tazobactam injection 3x2,25, PE 13 sessions, HD, 7Ü ES replacement, eculizumab	SDBY
14	During Salmonella species epidemics	Mesangial Proliferative Glomerulonephritis.	HD 8 sessions, PE 12 sessions 2Ü ES replacement, prednisolone 1mg/kg, Azathioprine 2x1, Valsartan 160mg 1x1	Normal
15	E coli	Not Performed	HD 6 sessions, Seftriaksonflk 2x1gr	Normal
16	Meme ca (gemcitabine)	Mesangial Proliferative Glomerulonephritis	HD 8 sessions, Plasma exchange 6 seans 4Ü ES replacement	Normal
17	Unclear	IgA nephropathy	HD 12 sessions, Plasma exchanges sessions, complete recovery of eculizumab in the absence of improvement	Normal
18	Unclear	Not Performed	HD, Plasma exchange 6 sessions, plus steroid, cyclophosphamide, eculizumab	ESRD

PE; Plasma exchange, HD; hemodialysis, ES; erythrocyte suspension, ESRD; end stage renal disease

produced Shiga toxin in Germany between May and June 2011, approximately one-fourth of the symptomatic cases developed HUS and 89% of the cases were adults. Another strain was responsible for this like Enteroaggregating E. coli O104: H4 producing Shiga toxin (10). Salmonella can rarely cause HUS. Shigella species in 7 cases, non-typhoidal salmonella in 9 cases and E coli in 11 cases were isolated in 73 cases of HUS (1980-1989) collected in India in 9 years. Shigella species in 7 cases, non-typhoidal salmonella in 9 cases and E coli in 11 cases were isolated in 73 cases of HUS (1980-1989) collected in India in 9 years. Of these, 50 had renal biopsies; cortical necrosis was detected in 20 (11). In gaita culture of one of our cases the salmonella species derived and in one case, in our city, it developed during a salmonella species outbreak.

aHUS develops as the result of uncontrolled activation of the alternative complement route. Mutations in the complement gene encoding complement C3, complement factor H (CFH), complement factor B (CFB), complement factor I (CFI), membrane cofactor protein (MCP) are associated with aHUS, it is estimated that 60% of cases with aHUS are caused by mutations in these genes (12-13). These mutations result in excessive complement activation and endothelial dysfunction leading to progressive dysregulation of the complement system.They play important role in complement regulation, inhibiting complement activation. Their homozygous or heterozygous mutations result in uncontrolled complement activation resulting in target organ damage (14-15). Besides, infectious diseases can trigger aHUS (16). Genetic mutation was observed in 3 cases; heterozygous CFB mutation, CFH polymorphism and no mutation was detected in one case.

The association of HUS with glomerulonephritis is rarely reported. The association of glomerulopathy and thrombotic microangiopathy, lupus nephritis, membranous GN, membranoproliferative GN, antiglomerular basement membrane, anti-neutrophil cytoplasmic antibody relation pauci-immun crescentic GN and post infectious GN were defined. Besides, focal segmental glomerulosclerosis, IgA and C3 glomerulonephritis related with HUS were defined (17-20).

In children having HUS related with Shiga-toxin producing E.Coli, the disease usually heals spontaneously. Typical HUS spontaneous healing occurs within 1-2 weeks. Early diagnosis and early treatment of acute renal failure, hypertension, and anemia and electrolyte impairment have significantly reduced mortality in recent years. In a meta-analysis that blends the results of twenty studies, it was emphasized that antibiotic treatment was not necessary because antibiotic use did not increase the development of HUS and would not change the course of colitis and it is extremely rare in the bacteraemia Shiga-toxin releasing E.Coli 0157/H7 infection (10). On the other hand, the antibiotic Shiga-toxin producing Sigella dysenteria is indicated for type-1 infections because bacterium is frequent and they can cause sepsis and death when not treated with appropriate antibiotics. Antimotility agents should not be given as bacterial and toxins inhibit the elimination by gaita but increase the likelihood of HUS. In adults with Shiga toxin-associated HUS, it was determined that plasma exchange significantly reduced mortality and ESRD rates in uncontrolled studies. In addition to comparing the results of two studies involving Shiga toxin-associated HUS cases with and without plasma exchange. Plasma exchange in HUS related with

Shiga toxin releasing E.Coli 0157:H7 has been shown to reduce mortality in adults. For this reason, plasma infusion and replacement with a prospective randomized study has not been shown to reduce mortality and ESRD rates, but plasma infusion and exchange should be performed especially in patients with severe renal impairment and central nervous system involvement (21). In our cases, liquid electrolyte implants were checked and given support. Most of our patients needed a suspension of erythrocytes. In severe cases (8 cases) plasma exchange was performed and prednisolone was started, followed by thrombocytopenia and LDH.

Thrombocytopenia improved in all cases. ESRD developed in 4 cases. Besides, patients in HD need were taken in HD. The German Nephrology Society has issued a treatment recommendation and recommended that antibiotics be discontinued. In severe HUS cases, administration of eculizumab, anti-C5 monoclonal antibody to the human, which inhibits terminal complement activation, is recommended (22). Eculizumab blocks cleavage of C5 the by preventing both formation of C5b-9 and the production of the anaphylatoxin C5a. Eculizumab treatment is given intravenously 600-900 mg once a week initially in adults. 900-1200 mg was given every 2 weeks to maintain therapy.

In conclusion, there are many etiologic factors that cause typical and / or atypical HUS. Among these, infections can trigger aHUS with causing typical HUS. In our cases, infection was detected in 5 patients. HUS and glomerulonephritis association were detected in 6 cases. In the treatment of patients, supportive treatment and underlying etiologic factor should be removed first. In patients who do not recover with supportive care, treatment with eculizumab needs.

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Compliance with Ethical Standards Ethical approval: The Ethics Committee of Cumhuriyet University, Faculty of Medicine approved the present study. The study was conducted in accordance with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Conflict of Interests

The authors have no conflict of interest.

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