Aplastic Anemia Frequency and Management in Pediatric Liver Transplantations Due to Non-A-E Hepatitis

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ABSTRACT

Background: *Hepatitis-associated aplastic anemia (HAAA) is a rare complication that presented with bone marrow failure after acute hepatitis. HAAA usually occurs in adolescent men within 1-6 months following hepatitis. Most of HAAA's etiology has non-A-E viral hepatitis.*

Methods: *Our retrospective study included patients with acute fulminant hepatitis who had been treated in Ege University Pediatric Gastroenterology, Hepatology and Nutrition Department and İzmir Kent Hospital Clinical, laboratory, and epidemiological data of the patients were collected from the files.*

Results: *In this study, 499 children underwent liver transplantation (LT) in two pediatric transplantation centers. Sixty-eight (13.6%) out of 499 patients, underwent liver transplantation due to fulminant hepatic failure (FHF). Therefore, a total of 64 patients (34 girls, 30 boys) with a diagnosis of FHF have included in the study. Thirty-two (50.0%) of 64 FHF were due to non-A-E hepatitis and 4 out of the 64 patients (6.2%) with FHF developed HAAA. All of the patients received prednisolone as immunosuppression treatment after LT. Three patients were also given Tacrolimus and 1 received an additional mycophenolate mofetil. One of the patients was given prednisolone and cyclosporine treatment without tacrolimus. Bone marrow transplantation was performed in 1 patient (25.0%). Two of the patients received immunosuppressive treatment including rabbit-derived anti-thymocyte globulin, cyclosporine, and initially prednisolone.*

Conclusion: *In children who underwent liver transplantation for non-A-E FHF are at high risk to develop aplastic anemia. The clinicians should be alert after orthotropic liver transplantation patient could develop aplastic anemia and early treatment with immunosuppressive therapies result in a more successful outcome.*

Keywords: *Liver transplant, pediatric, non-A-E, hepatitis*

BACKGROUND

Hepatitis-associated aplastic anemia (HAAA) is a rare complication that presented with bone marrow failure after acute hepatitis.[1] It can develop in 0.03-0.2% of acute hepatitis.[2] HAAA usually occurs in male adolescents within 1-6 months after hepatitis.[1] Hepatitis viruses A, B, C, D, E, and G, as well as parvovirus, transfusion-transmitted virus, and non-A-E hepatitis viruses, can cause HAAA.[3,4] However, most of HAAA's etiology has seronegative viral hepatitis.[1] The pathogenesis is not fully known, and it is thought to develop as a result of immune dysregulation following acute hepatitis, and if not treated, the mortality is high.[1,2,5] It is usually treated with immunosuppressive agents, stem cell transplantation is preferred if matched sibling donor is available.[1] The aim of our study is to determine the frequency of aplastic anemia in patients with liver transplantation (LT) due to fulminant hepatic failure (FHF) at Ege University Pediatric Gastroenterology, Hepatology and Nutrition Department and İzmir Kent Hospital between 1997 and 2018. Treatment response, clinical characteristics, and prognosis of patients with HAAA were targeted.

MATERIALS AND METHODS

Our retrospective study included patients with acute fulminant hepatitis who had been treated in Ege University Pediatric Gastroenterology, Hepatology and Nutrition Department and İzmir Kent Hospital between the dates of 1997 and 2018. Clinical, laboratory, and epidemiological data of the patients were collected from the files in order to evaluate the risk factors of HAAA development. Non-A-E hepatitis diagnosed with metabolic disease, autoimmune hepatitis, toxin exposure, and cytomegalovirus, hepatitis A-B-C virus, Ebstein-Barr virus, herpes simplex virus, human immunodeficiency virus infection were excluded. FHF was defined as severe liver impairment

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lasting < 8 weeks in a child with no previous history of liver disease, with coagulopathy (international normalized ratio [INR] >2), with or without encephalopathy. Patients underwent LT with this indication. The assessment of encephalopathy was based on clinical assessment and neurological signs. A multidisciplinary team including a transplant surgeon, hepatologist, transplant coordinator, psychologist meets with the family and explains the risks and benefits of transplantation for the child. Diagnosis of aplastic anemia (AA), patients with at least 2 of the criteria of peripheral blood: neutrophil count below 500/mm^3, platelet count below 20 000/mm^3, reticulocyte count below 1% with a bone marrow cellularity below 30%. Intermittent whole blood count, biochemistry, blood levels of immunosuppressive drugs, and bleeding parameters were taken from the patients during the follow-up. Informed consent did not take from patient's family because data were collected retrospectively. Ethics Committee approval was taken from Ege University, and its number is E.94008.

Statistical Analysis

SPSS (Statistical Package for Social Sciences) 22.0 for Windows program was used for statistical analysis. Significance was accepted as $P < .05$. Mean, standard deviation, and percentage distribution data were used for descriptive data. A chi-squared test was applied for comparison of patients with HAAA or no HAAA.

RESULTS

From 1997 to 2018, 499 children underwent liver transplantation in two pediatric transplantation centers. Sixty-eight (13.6%) out of 499 patients, underwent liver transplantation due to FHF. Four patients with a diagnosis of FHF have excluded from the study because the data could not be reached. Therefore, a total of 64 patients (34 girls, 30 boys) with a diagnosis of FHF have included in the study. Thirty-two (50.0%) of 64 FHF were due to non-A-E hepatitis. The remaining 14 (21.9%) patients had hepatitis A, 4 (6.2%) had Wilson's disease, 13 (20.3%) had toxic hepatitis, and 1 (1.6%) had autoimmune hepatitis.

MAIN POINTS

- *Hepatitis-related aplastic anemia could develop after seronegative viral hepatitis.*
- *Hepatitis-related aplastic anemia could be fatal if left untreated.*
- *Hepatitis-related aplastic anemia should always be kept in mind when developing cytopenias during and after viral hepatitis.*

Table 1. Initial Laboratory Tests of the Patients

	Case 1	Case 2	Case 3	Case 4
ALT (U/L)	520	972	496	1106
AST (U/L)	385	562	666	1030
Total bilirubin (mg/dL)	28.0	29.9	12.4	17.4
Direct bilirubin (mg/dL)	9.7	27.8	11.1	14.3
INR	2.1	2.37	7.27	1.65
LDH	249	450	350	354
WBC	7800	9960	18 791	3100
HGB	10.8	12.2	8.6	9.1
HTC	31.6	37.7	25.8	29.4
MCV	69.5	76.9	27.4	81.7
MCHC	34.2	33.0	33.3	31.0
PLT	251 000	345 000	539 000	291 000

ALT, alanine transaminase; AST, aspartate aminotransferase; INR, international normalized ratio; LDH, lactate dehydrogenase; WBC, white blood cell; HGB, hemoglobin; HTC, hematocrit; MCV, mean corpuscular volume; MCHC, mean corpuscular hemoglobin concentration; PLT, platelets.

Characteristics of the Patients With HAAA

Four out of the 64 patients (6.2%) with FHF developed HAAA. There was no other patient who developed HAAA and those who had an LT for any reason at these centers. The underlying cause of FHF in all of those 4 patients was non-A-E hepatitis. Two of the patients were girls. The average age is 6.5 years (2-10 years). Initial laboratory tests of the patients are shown in Table 1.

All of these patients' transplantation was performed from a living-donor. The time of onset of pancytopenia was detected as a median of 20.5 days (range 3-270) after LT. All patients received prednisolone as immunosuppression treatment after LT. Three patients were also given tacrolimus and 1 received an additional mycophenolate mofetil. One of the patients was given prednisolone and cyclosporin treatment without tacrolimus.

Treatment of the Patients With HAAA

Bone marrow transplantation was performed in 1 patient (25.0%). Two patients received immunosuppressive treatment including anti-thymocyte globulin, cyclosporine, and initially prednisolone. One patient died 54 days after LT, despite intensive supportive treatment. This patient could not be given any specific treatment for HAAA. The general characteristics of the patients are given in Table 2.

Table 2. General Characteristics of the Patients

	Case 1	Case 2	Case 3	Case 4
Sex-age	F-10 years old	M-6 years old	F-8 years old	M-2 years old
Type of liver transplantation	Living donor	Living donor	Living donor	Living donor
Time of pancytopenia	Post-transplantation 3rd day	Post-transplantation 30th day	Post-transplantation 9th month	Post-transplantation 11th day
Treatment	- Tacrolimus - Prednisolone	- Tacrolimus	- Tacrolimus - Mycophenolate Mofetil - Prednisolone	- Cyclosporine A - Prednisolone
Stem cell-transmitting blood group-receiver blood Group		O Rh – O Rh +		
Treatment of HAAA	- Erythrocyte, granulocyte, thrombocyte transfusion - Large spectrum antibiotic - G-CSF	- G-CSF - Stem cell transplantation	- G-CSF - RATG - Cyclosporine - Prednisolone	- G-CSF - RATG - Cyclosporine - Prednisolone
Final status	Exitus (septic shock)	Alive	Alive	Alive

F, female; M, male; HAAA, hepatitis-related aplastic anemia; G-CSF, granulocyte colony-stimulating factor; RATG, rabbit anti-thymocyte globulin.

There was no significant difference between the initial laboratory findings of the patients who developed HAAA and those who did not develop HAAA. A comparison of these two groups presented in Table 3.

DISCUSSION

The first reports of HAAA following liver transplantation were, respectively, in 1955 by Lorenz and Quaiser and in 1987 by Stock.[6] Aplastic anemia is well described in children following liver transplantation for FHF secondary to seronegative hepatitis.[1,7] The relationship between aplastic anemia and viral hepatitis is well known.[1] The incidence of aplastic anemia associated with acute hepatitis of known etiology is 0.07% and following liver transplantation for such known hepatitis is 0.007%. However, the incidence of aplastic anemia is much higher in association with seronegative hepatitis (33% in children and 5% in adults) and following liver transplantation for seronegative hepatitis (28%).[6,8] HAAA has a high mortality rate.[7] Pathogenesis is not fully known and it is thought to develop as an end result of immune dysregulation following acute hepatitis and if not treated.[1,2,5] Activated T1 lymphocytes have been described as effector cells in most cases, the disease can be treated with combined immunosuppressive therapy or allogeneic hematopoietic stem cell transplantation.[9] The proposed pathogenesis is that there are indirect bone marrow suppression and hepatitis due to viral-induced proliferation of activated CD8 cells.[6,8] Bone marrow dysfunction rarely precedes but usually occurs either with hepatitis or 1 to 7 weeks after liver transplantation.

The etiology of 32 (50.0%) of 64 patients with liver transplantation who were diagnosed with fulminant hepatitis was non-A-E hepatitis 14 (21.9%) of all patients had hepatitis A. Consistent with our study, Shouval et al.[10] found that hepatitis A was found in the etiology of 30.8% of the patients. In our study, aplastic anemia developed in 4 of 32 patients (12.5 %). HAAA was observed in 23.2-33% of patients who underwent liver transplantation for fulminant non-A-E hepatitis.[6,11] In addition, Cattral et al.[11] reported that 6 (33.0%) out of 18 children and 1 (5.0%) out of 19 adults undergoing liver transplantation for HAAA due to seronegative hepatitis.

The association of aplastic anemia and seronegative hepatitis is commoner in male adolescents.[6] In our study, the male/female ratio was 2/2. The average age is 6.5 years (2-10 years). Mali et al. were reported a 10-year-old boy with HAAA.[12] Perkins et al. were presented a 3.5-year-old boy.[13] Itterbeek et al. was reported that patient's mean age was 10.0 years, male/female ratio was 23/5.[6] This gender difference may be related to the low number of our patients.

In the study, the median time between liver transplantation and the onset of pancytopenia was 20.5 days. Itterbeek et al was presented 10.3 days, Mali et al. were reported that the patient's pancytopenia had been detected at admission, at Perkins et al.'s study 60 days later after transplantation.[6,12,13]

Table 3. Differences Between Fulminant Hepatic Failure Patients With and Without HAAA

	Patients Without HAAA	Patients With HAAA	*P*
Age [median (range)] (month)	48 (7-216)	72 (24-120)	NS
Gender (girl/boy)	32/28	2/2	NS
Cause of FHF			
Non-A-E hepatitis	28	4	
Hepatitis A	14		
Toxic hepatitis	13		
Wilson disease	4		
Autoimmune hepatitis	1		
Encephalopathy grade median(range)	2	1.5	NS
Type of liver transplantation			
Living-related donor	46	4	NS
Living unrelated	1	0	NS
Cadaveric	13	0	NS
Initial laboratory findings			
ALT	746.0	746.4	NS
AST	1093.1	614.4	NS
Albumin	3.6	3.5	NS
Total bilirubin	15.7	22.7	NS
Direct bilirubin	8.8	12.7	NS
LDH	762.0	352.0	NS
INR	3.3	2.2	NS
WBC	9625.0	8880.0	NS
HGB	10.0	9.9	NS
HCT	29.9	30.5	NS
MCV	79.7	73.2	NS
MCHC	33.2	33.1	NS
PLT	238 500.0	318 000.0	NS
Immunosuppressive treatment after Liver transplantation			
Tacrolimus	53	2	<.05
Tacrolimus + mycophenolate mofetil	2	1	
Cyclosporine	2	0	
Cyclosporine + sirolimus	0	1	
Sirolimus	3	0	
Survival	46 (76.7%)	3 (75.0%)	NS
Child-Pugh	10.7 ± 1.33	10.25 ± 1.7	NS
MELD	38.1 ± 5.7		
PELD	31.3 ± 8.2	29.2 ± 11.1	NS

NS, not significant; ALT, alanine transaminase; AST, aspartate aminotransferase; INR, international normalized ratio; LDH, lactate dehydrogenase; WBC, white blood cell; HGB, hemoglobin; HTC, hematocrit; MCV, mean corpuscular volume; MCHC, mean corpuscular hemoglobin concentration; PLT, platelets; HAAA, hepatitis-related aplastic anemia; FHF, fulminant hepatic failure; MELD, the model for end-stage liver disease; PELD, the pediatric end-stage liver disease.

Spontaneous myeloid recovery on maintenance immunosuppressant takes up to 6 months and has 50.0% mortality due to infections and bleeding.[8] Mortality rate of our study was 25.0% due to infections. The reported mortality rate was between 33.0% and 44.4%.[6,11,14] The low mortality rate in our study may be related to early diagnosis due to awareness of HAAA.

A wide range of treatments have been advocated for aplastic anemia including sibling matched bone marrow transplantation, immunotherapy, corticosteroids, and granulocyte colony-stimulating factors.[15] One of 4 patients underwent bone marrow transplantation by virtue of immunosuppressive resistance to severe aplastic anemia. Perkins et al. and Stachel et al. were reported that 2- and 3.5-year-old-boy underwent bone marrow transplantation.[13,16] Two of the patients benefited from combined immunosuppressive therapy. In the case reports of Sato et al. and Mali et al., respectively, 2- and 10-year-old patients benefited from combined immunosuppressive treatment and could not be hematopoietic stem cell transplantation.[3,12] Rajwal et al. was presented that 14 years old boy was healed due to ımmunosuppressive treatment.[15] Sanches et al. was reported 2 cases whose HAAA was recovered due to immunosuppressive treatment [antithymocyte globulin (15 mg/kg/day) and methylprednisolone (2 mg/kg/day) for 10 days, and cyclosporine (9-12 mg/kg/day)].[7] Hepatitis-related aplastic anemia could develop after seronegative viral hepatitis and it could be fatal if left untreated. For this reason, it should always be kept in mind when developing cytopenias during and after viral hepatitis.

Ethics Committee Approval: Ethics committee approval was received for this study from the Ege University, E.94008.

Informed Consent: Informed consent is not necessary due to the retrospective nature of this study.

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