ORIGINAL ARTICLE
ORİJİNAL ARAŞTIRMA

Retrospective Evaluation of Child Cases Followed with the Prediagnosis of Crimean-Congo Hemorrhagic Fever

Kırım Kongo Kanamalı Ateşi Ön Tanısı ile Takip Edilmiş Çocuk Vakaların Retrospektif Değerlendirilmesi

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ABSTRACT

Aim: The aim of our study is to evaluate the clinical, demographic and laboratory findings of the patients who were followed up with the diagnosis of Crimean-Congo hemorrhagic fever (CCHF) in Gaziosmanpaşa University Medical Faculty Child Health and Diseases Service. This study was carried out with the aim of this study was to observe the importance of early diagnosis, observing the effects of the supportive treatment, documenting hospitalization time and the complications during the treatment.

Material and Method: The study was carried out in a single center, Gaziosmanpaşa University Faculty of Medicine, Pediatrics Service in accordance with the Declaration of Helsinki Principles. Medical records of patients who were followed up with a prediagnosis of CCHF between January 2012 and July 2016 were retrospectively reviewed. Epidemiological, demographic and clinical characteristics, laboratory data, treatment methods and results of all cases were evaluated from patient files.

Results: Between January 2012 and July 2016, a total of 100 patients with CCHF were detected. 52 % of the patients came from rural areas. The most applications were in April and June (69 %) months. 100 % of the patients had a history of contact with ticks. The main symptoms and signs were fever (38%), haematological findings (34%), malaise (47 %), abdominal pain (11 %), headache (25 %) and muscle pain (44 %). At the time of admission to the hospital, 6 % of patients had thrombocytopenia, 26 % had leukopenia, 26 % had elevated aspartate aminotransferase (AST), 12 % had elevated alanine aminotransferase (ALT), 44 % had elevated lactate dehydrogenase (LDH), 70 % had elevated creatine phosphokinase (CPK), 8 % had prolonged prothrombin time (PT), prolonged active partial thromboplastin time (aPTT) in 28 % and elevated international normalised ratio (INR) in 13 %. All patients underwent liquid-electrolyte therapy for support, 5 % aphasic platelet suspension, 13 % fresh frozen plasma, 12 % repeated erythrocyte suspension, and 13 % received ribavirin treatment. All of the patients who were included in the study were discharged with recovery.

Conclusion: In conclusion, clinical manifestations of CCHF are similar to adults in children and CCHF is more favorable in children. There is no definitive proven treatment method yet, and most of the treatment is supportive treatment.

Keywords: Crimean-Congo hemorrhagic fever, child, supportive treatment

ÖZ

Amaç: Çalışmamızın amacı Gaziosmanpaşa Üniversitesi Tıp Fakültesi Çocuk Sağlığı ve Hastalıkları Servisinde Kırım-Kongo kanamalı ateşi (KKKA) tanısı ile takip edilen hastaların klinik, demografik ve laboratuvar bulgularını değerlendirmektir. Bu çalışma erken tanının önemini, uygulanan destekleyici tedavinin hastanede kalış süresini kısaltmaya ve komplikasyon gelişimini önlemeye etkisini gözlemlemek amacıyla yapılmıştır.

Gereç ve Yöntem: Çalışma Helsinki İlkeler Deklarasyonu'na uygun, tek merkezli olarak Gaziosmanpaşa Üniversitesi Tıp Fakültesi Çocuk Sağlığı ve Hastalıkları servisinde gerçekleştirilmiştir. Ocak 2012 ile Temmuz 2016 arasında KKKA ön tanısı ile takip edilmiş olan hastaların tıbbi kayıtları geriye dönük olarak incelenmiştir. Tüm olguların epidemiyolojik, demografik ve klinik özellikleri, laboratuvar verileri, tedavi yöntemleri ve sonuçları hasta dosyalarından değerlendirilmiştir.

Bulgular: Ocak 2012-Temmuz 2016 tarihleri arasında KKKA öntanılı 100 hasta tespit edildi. Hastaların %52' si kırsal kesimden geliyordu. En çok başvuru Nisan ve Haziran (%69) ayları aralığında idi. Hastaların %100'ünde kene ile temas öyküsü vardı. Hastaneye başvuru esnasında başlıca semptomlar ve bulgular ateş (%38), hematolojik bulgular (%34), halsizlik (%47), karın ağrısı (%11), başağrısı (%25), kas ağrısı (%44) idi. Hastaneye başvuru esnasında hastalarda %6 trombositopeni, %26 lökopeni, %26 yüksek AST, %12 yüksek ALT, %44 yüksek LDH, %70 yüksek CPK, %8 uzamış PT, %28 uzamış PTT, %13 yüksek INR saptandı. Hastaların tamamı destek amaçlı sıvı-elektrolit tedavisi, %5' i aferezli trombosit süspansiyonu, %13'ü taze donmuş plazma, %12'si tekrarlayan sayıda eritrosit süspansiyonu, %13'ü ribavirin tedavisi aldı. Takibe aldığımız hastalarımız şifa ile taburcu edildi.

Sonuç: Sonuç olarak, KKKA klinik bulguları çocuklarda erişkinlere benzerdir ve ancak KKKA çocuklardaki seyri daha iyidir. Etkinliği kesin olarak kanıtlanmış bir tedavi methodu henüz bulunmamakta olup tedavinin en büyük bölümünü destek tedavisi oluşturmaktadır.

Anahtar Kelimeler: Kırım-Kongo Kanamalı ateşi, çocuk, destek tedavi

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INTRODUCTION

Crimean-Congo Hemorrhagic Fever (CCHF) is a zoonotic Viral Hemorrhagic Fever (VHF) disease, which is an important cause of mortality by causing acute high fever and bleeding and even shock in humans (1). CCHF is a viral infection originating from the Nairovirus species of the Bunyaviridae family, which has been identified in approximately 30 countries in Asia, Africa, Eastern Europe and the Middle East, causing an important public health problem (1,2,3). Although the first case in Turkey was reported in Tokat in 2002, epidemics have been reported in neighboring countries since 1970 (4,5,6). Despite the fact that Turkey is the country with the highest number of cases in the world, the number of publications in pediatric cases regarding CCHF, which is an important public health problem in all seasons, is quite limited. Although human-to-human nosocomial transmission has been reported, the mode of transmission of the virus to humans is usually by contact with infected ticks or by contact with bodily fluids of infected animals. The virus causes a serious clinical course with a mortality of 3-30% in humans (7). Endothelial dysfunction due to vascular damage causes bleeding and this is the most common cause of death due to the disease. Sudden fever, malaise, anorexia, myalgia, cough, headache and abdominal pain are frequently seen in the clinic of the disease. Mortality risk is increased in cases with disseminated intravascular coagulopathy (DIC) and the worst prognosis belongs to this group (8). In laboratory examinations, leukopenia and thrombocytopenia due to bone marrow involvement, elevation in muscle and liver enzymes due to viral cytopathy; elongation is observed in coagulation parameters (9). In order to make the diagnosis, it is important to detect virus isolation, antigen tests or reverse transcriptase polymerase chain reaction (RT-PCR) in the first week of the application, and then detect the antibodies developed against the virus by Enzyme Linked Immuno Sorbent Assay (ELISA) or Indirect Fluorescent Antibody (IFA) method (10).

MATERIAL AND METHOD

The study was carried out in accordance with the Declaration of Helsinki Principles. All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. The study was conducted as a single center, retrospective chart review study. Children between 0 and 18 years of age accepted by the tick bite from April 2012 to June 2016 in Gaziosmanpaşa University Medical Faculty Child Health and Diseases Service were evaluated. The data were reviewed retrospectively using the Hospital Information Management System.

Epidemiological data of all patients; age, gender, province, district, contact season, presence of a similar case in the family, extraction of the tick, history of a chronic disease, history of tick contact (tick attachment and/or suspected contact), clinical and laboratory data, fever, anorexia, weakness, headache, nausea-vomiting, abdominal pain, diarrhea, hematological findings as LDH, ALT, AST , CPK, white blood count (WBC), mean platelet volume (MPV), hemoglobin (Hb), platelet (PLT), c-reactive protein (CRP), PT, aPTT, INR, sedimentation; data on treatment; whether oral ribavirin was administered, blood and blood products (fresh frozen plasma, erythrocyte suspension, platelet suspension, random-apheresis) and outcome data; cure or death were analyzed for each patient. Hematological symptoms such as epistaxis, hematuria, melena, gingival bleeding and skin rash were documented.

Statistical Analysis

The statistical data analysis was performed using IBM SPSS for Windows (IBM statistics for Windows version 20, IBM Corporation, Armonk, New York, United States). In descriptive statistics of the data, mean±standart deviation for normally distributed variables and median (min-max) values for non-normally distributed variables were used, categorical variables were given as n (%). The qualitative data were analyzed by chi-square test, as appropriate. $P<0.05$ was accepted as a cutoff value for statistical significance.

RESULTS

100 patients who applied with the complaint of tick bite between April 2012 and June 2016 were included in the study. Polymerase chain reaction (PCR) test positivity was detected in 16 (16%) of these patients and as the 'CCHF group'; Cases that were PCR negative and were not sent PCR in their outpatient follow-up were considered as the 'tick attachment group'. These two groups were compared in terms of demographic, clinical and laboratory characteristics. (**Table 1**).

Considering the distribution, there were 24 patients under 5 years of age (24%), 22 patients between the ages of 5 and 10 years old (22%), and 54 patients older than 10 years old. There was no significant difference between the positive and negative groups with PCR results according to gender and age groups (p=0.542, p=0.052). Considering the residential areas of the patients, 52 (52%) of 100 patients lived in rural areas. All patients (100%) with positive PCR results lived in rural areas. This relationship was considered significant after it was determined that all PCR-positive cases lived in rural areas (p<0.001). In cases whose diagnosis was confirmed by PCR and excluded, CCHF patients were observed to remove the tick by themselves. When the admission periods of the patients were examined, no

significant correlation was found between PCR positive detection (p=0.626). On the other hand, none of our 16 cases whose diagnosis was confirmed by PCR applied to the health institution in the first 24 hours after noticing the tick.

Table 1. Demographic and epidemiological characteristics of patients

	PCR		X2	p
	Positive (n=16,%)	**Attachment (n=84,%)**		
Gender			0.373	0.542
Female	7 (43.8)	27 (32.1)		
Male	9 (56.3)	57 (67.9)		
Age			5.901	0.052
<5	1 (4.2)	23 (95.8)		
5-10	2 (9.1)	20 (90.9)		
>10	13 (24.1)	41 (75.9)		
Residential			17.582	<0.001
Rural Area	16 (100)	36 (42.9)		
Rural Area Visit	-	24 (28.6)		
Other	-	24 (28.6)		
Extraction			6.547	0.038
By themselves	14 (87.5)	45 (53.6)		
At Hospital	1 (6.3)	28 (33.3)		
Applied without tick penetration	1 (6.3)	11 (13.1)		
Season			1.751	0.626
January – March	-	5 (6)		
April - June	11 (68.8)	58 (69)		
July- September	5 (31.3)	19 (22.6)		
October –December	-	2 (2.4)		
Family History			0.001	0.999
Positive	6 (37.5)	31 (36.9)		
Negative	10 (62.5)	53 (63.1)		
Hospital admission			21.859	<0.001
Immediately	-	37 (44)		
Within three days	5 (31.3)	33 (39.3)		
After three days	11 (68.8)	14 (16.7)		

Pcr : polymerase chain reaction

When the clinical characteristics of the patients at the time of admission are examined in **Table 2**; fever in 38 (38%), headache in 25 (25%), myalgia in 44 (44%), malaise in 47 (47%), abdominal pain in 11 (11%). Since the fever symptom lasted less than 1 week in patients who applied with the complaint of fever, they were not examined for hemophagocytic lymphohistiocytosis (HLH), and fibrinogen triglyceride and ferritin values were not tested. Hematological symptoms such as epistaxis, hematuria, melena, gingival bleeding and skin rash were present in 30 (30%) (**Table 2**). Presence of fever, headache, myalgia, malaise, abdominal pain and hematological symptoms in CCHF clinic were considered statistically significant. (p<0.001, p<0.001, p<0.001, p<0.001, p=0.014, p<0.001).

Table 2. Clinical characteristics of the patients at the time of admission

		Pcr		X2	p
		Positive n=16 (%)	**Negative n=84 (%)**		
Fever	Present	16 (100)	22 (26.2)	0.282	<0.001
	Absent	-	62 (73.8)		
Headache	Present	12 (75)	(15.5)	-	<0.001
	Absent	4 (25)	71 (84.5)		
Myalgja	Present	16 (100)	28 (33.3)	21.612	<0.001
	Absent	-	56 (66.7)		
Fatigue	Present	16 (100)	31 (36.9)	19.021	<0.001
	Absent	-	53 (63.1)		
Abdominal Pain	Present	5 (31,3)	6 (7.1)	-	0.014*
	Absent	11 (68,8)	78 (92.9)		
Hematological symptom *		12 (75)	18 (25)	47.509	<0.001
Hospitalization Indication	CCHF PCR+	16 (100)	-	86.7722	<0.001
	Tick bite	-	13 (15.5)		
	Other *	-	11 (13.1)		
	Outpatient	-	64 (76.2)		
Hospitalization Time	0-3 days	-	4 (4.8)	41.42	<0.001
	3-10 days	8 (50)	10 (11.9)		
	>10 days	8 (50)	6 (7.1)		

* epistaxis, hematuria, melena, gingival bleeding, rash, CCHF: Crimean-Congo hemorrhagic fever

The patients in the study had thrombocytopenia in 28%, leukopenia in 26%, low Hb in 23%, elevated ALT in 25%, elevated AST in 30%, elevated LDH in %11, elevated CPK in 52%, prolonged PT in 70%, prolonged PTT in 38%, elevated INR in 21% ; 10% of the patients had elevated sediment levels and 21% had elevated CRP levels at initial laboratory data. The definitive diagnosis of the patients was made by PCR test, and there was no significant difference between Hgb and Hct values of PCR+ and PCR- patients (p>0.001), a statistically significant difference was found between the white blood cell measurements, and significant difference was found in the platelet count (p<0.001). With this finding, leukopenia and thrombocytopenia were considered significant in laboratory values of the patient with CCHF diagnosis. Of the 36 hospitalized and followed-up patients, 16 (100%) were included in the group whose CCHF diagnosis was confirmed by PCR. 8 (50%) of the patients with positive PCR analysis were hospitalized for 3-10 days, and the other 8 (50%) were hospitalized for longer than 10 days. Follow-up of 64 patients (76,2 %) who presented with tick bite was performed from the outpatient clinic and emergency service, without admission to the inpatient service.

When we compared the INR values, a statistically significant difference was detected. In these cases, measurement of the INR value within the normal range at discharge suggested that the transient prolongation in coagulation parameters was associated with hematological symptoms. (mean square: 0,778; F: 9,178; p=0,008) (**Table 3**).

Table 3. INR Measurements at Admission and Discharge in Patients with CCHF Diagnosis

(J) Time	Mean Difference (I-J)	Std. Error	Significant.[a]	95% Confidence Interval for Difference[a]	
				Lower bound	Upper bound
Admission	0.29	0.15	0.229	-0.12	0.069
Discharge	0.289*	0.089	0.017	0.048	0.529

CCHF: Crimean-Congo Hemorrhagic Fever, INR:International normalised ratio, Based on estimated marginal means, *. The mean difference is significant at the 05 level. A. Adjustment for multiple comparisons: Bonferroni

When we compared the values of transaminase and muscle enzymes at admission and discharge, there was no significant difference in ALT value, but a significant difference in AST value. (mean square: 228858.336; F: 18.216; p<0.001); Significant difference was also found in CK and LDH values (mean square:1696108.193/1132555.607; F: 15.197/12.593; p<0.001/ p=0.002). For the acute phase reactants CRP and sedimentation, there was no significant difference between PCR positive and negative patients. Oral ribavirin therapy was given to 14 selected patients with bad prognosis. It was confirmed by PCR that 12 (75%) of our selected patients who were started on ribavirin were CCHF. With this finding, we determined that ribavirin was used appropriately in selected patients (p<0.001). It was determined that appropriate supportive treatment was given in all 36 cases followed up by hospitalization, and 13 of the patients were transfused with blood products. (**Table 4**).

Table 4. Ribavirin use in selected cases-Evaluation of support treatment protocol

	PCR		X²	p
	Positive n=16 (%)	Attachment n=84 (%)		
Ribavirin Usage			-	<0.001
Positive	12 (75)	(2.4)		
Negative	4 (25)	82(97.6)		
Transfusion			-	<0.001
Erythrocyte Suspension	-	-		
Fresh Frozen Plasma	1 (6.3)	-		
Apheresis Platelet	-	-		
Random Platelet	4 (25)	1 (1.2)		
Repeated Transfusion	8 (50)	3 (3.6)		
None	3 (18.8)	80 (95.2)		

Pcr : polymerase chain reaction

DISCUSSION

Studies on CCHF are mostly based on adults all over the world. Studies on the pediatric age group are very rare in the literature. In this study, epidemiological, clinical and laboratory characteristics and results of pediatric patients from the Central Black Sea region, where CCHF is endemic, were evaluated retrospectively. We think that tick contact history is very important in terms of transmission routes of CCHF in our region and that patients with suspected CCHF should be questioned while taking their anamnesis. Our study was carried out in an endemic region and the follow-up of patients who were thought to have CCHF as clinical and laboratory was carried out by hospitalization. Pcr positivity and hemorrhagic symptoms were accepted as hospitalization indications.

Crimean-Congo hemorrhagic fever is known to have seasonal characteristics. June-September is the period when epidemics are common. However, this situation may vary according to the region (11). CCHF is frequently seen in endemic areas in our country, in the spring and summer months when vector ticks become active (12). The most frequent application of our patients was between April and September (most frequently in June).

Tuygun et al. in their retrospective study, which included 50 out of two hundred pediatric patients who applied from the endemic regions of Southern Black Sea, Central and Northeast Anatolia in the spring-summer months between 2005 and 2010, no significant difference was found in terms of age groups and gender (13). Child patients younger than 18 years of age, who are generally in the school age group, were included in our study. Although there was an increase in the number of cases seen in adolescence between pcr positive and pcr negative patients no statistically significant difference was found.

Headache is often reported as the first complaint in CCHF disease. Other clinical findings may include high fever, fatigue, weakness, abdominal pain, widespread muscle and joint pain, and even changes in consciousness at different stages in some patients. Conjunctival hyperemia and ecchymoses of various sizes may occur in patients (14,15). Patients have a tendency to bleed; hemorrhagic symptoms are observed such as hematemesis, epistaxis, melena, hematuria, vaginal bleeding, gingival bleeding, and bleeding into internal organs (5,16). In a study conducted with children in Iran, the most common presentation symptoms and findings were fever (88.2%), nausea (61.8%), myalgia (70.6%), bleeding (70.6%), and headache (64.7%) (17). Our study was concluded in accordance with the literature in terms of clinical findings.

In addition to thrombocytopenia and leukopenia, increased liver enzymes ALT and AST, CPK, LDH and prolonged coagulation parameters can be detected in the laboratory findings of the patients at the time of admission. A general feature of CCHFV infection is thrombocytopenia (2). Dilber et al. reported 70% leukopenia, 50% CPK and ALT elevation, and 65% thrombocytopenia in 21 pediatric patients. Anemia developed in 28.5% of the patients, bleeding from various origins in 42.8% and thrombocytopenia in

23.8% of the patients during follow-up. They reported pulmonary hemorrhage in two of their cases (18). Sharifi-Mood et al. stated that 44% of their cases had elevated transaminase values (17). In our study, at the time of admission, 28% of the patients had thrombocytopenia, 30% had elevated AST, 26% had leukopenia, 38.5% had elevated INR, 35.9% had elevated CPK, 28.2% had elevated ALT, and 70% Prolonged PTT was found in 21% of patients. However, there are no laboratory criteria used to predict the diagnosis for CCHF. In countries where CCHF disease is endemic, such as our country, it is important to recognize the disease early and take the necessary precautions. The only study to interpret the factors affecting mortality in children was conducted in Iran, and it was reported that impaired consciousness is the only independent risk factor associated with mortality at hospital admission (17). Since there was no case lost in our study, the factors affecting mortality could not be evaluated.

The main goal in the management of the disease is general supportive treatment (12). Close monitoring of laboratory parameters is necessary in order to perform blood product replacement when necessary. Apart from general supportive treatment, ribavirin is the only antiviral drug that can be used in the treatment of VHF syndromes. In a study conducted by Sharifi-Mood et al. with 34 children and adolescents from Iran, 26.5% mortality was reported despite ribavirin treatment (17). Izadi et al. reported that the positive effect of ribavirin from the same country is related to the time of initiation of treatment and if it is applied during the viremia period, it will be effective in bleeding and mortality (19). Ergönül et al. reported that ribavirin treatment in the early phase of the disease may reduce mortality (5). Tezer et al. in a study they conducted in our country, they added ribavirin to their treatment options because they had bad prognosis criteria in 7 patients and reported that they did not experience any side effects (20). In our study, 14 patients received ribavirin treatment (14%). 12 patients received supportive treatment in addition to ribavirin treatment (85.7 %). In terms of the limitations of our study, it may not be helpful for cases in the initial period of the disease, as it was conducted in a single-center, retrospective and tertiary healthcare institution.

CONCLUSION

In the Crimean-Congo Hemorrhagic Fever disease, the pediatric age group is a special patient group and precautions for prevention and control must be taken. In order to prevent infection and manage it well, it is important not to be late in diagnosis and treatment. Early diagnosis is important for the patient as well as family members and healthcare professionals who are in contact with the patient. In terms of clinical features, it shares a lot with other viral hemorrhagic fever diseases. In this respect, it is important to remember the diagnosis and make a differential diagnosis. Laboratory findings are valuable in terms of clinical follow-up and prognosis of the patient. In supportive treatment, blood product transfusion with fluid-electrolyte therapy and monitoring of laboratory parameters has an important place. Cases with bad prognosis criteria should be followed closely as critically ill patients in the intensive care unit, and ribavirin treatment should be kept in mind in selected cases. We did not have any patient who applied with repetition of complaints after discharge, but one of our patients living in rural areas applied to our clinic again after two years with a tick bite. We did not lose any patient in our 4-year clinical follow-up. All 100 cases were discharged with cure.

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