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Various clinical conditions can mimic Crimean-Congo hemorrhagic fever in pediatric patients in endemic regions

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Summary Crimean-Congo hemorrhagic fever (CCHF) is a tick-borne disease with high mortality. Many disorders can mimic CCHF. It is important to recognize the condition and to perform differential diagnosis in endemic countries. Twenty-one children aged 18 years or less with a preliminary diagnosis of CCHF were retrospectively evaluated. Real-time PCR and a confirmatory indirect immunofluorescence assay for negative results were performed. The diagnoses determined that 9 patients had (42.9%) CCHF; 7 patients had (33.3%) viral upper respiratory tract infections (URTI); 2 patients had (9.5%) brucellosis; 1 patients had (4.7%) periodic fever, aphthous stomatitis, pharyngitis, and adenitis (PFAPA) syndrome episode; 1 patient had (4.7%) cerebral palsy, diabetes insipidus, acute gastroenteritis, and hypernatremic dehydration; and 1 patient had (4.7%) cellulitis after a tick bite. The mean age of patients with CCHF was greater than that of the other patients (116.1 ± 53.6 vs. 94.1 ± 52.1 months, $p = 0.02$). Seventeen (81%) of the children included had a history of tick bites, 2 (9.5%) had a history of contact with a patient with CCHF, and 2 (9.5%) had no exposure, but were living in an endemic region. Three patients had an underlying disorder: cerebral palsy and diabetes insipidus, epilepsy, or PFAPA. All of the children experienced fever. Other frequent symptoms were malaise, diarrhea, vomiting, and abdominal pain, but none of these differed statistically between the patient groups. CCHF patients had a longer mean duration of symptoms (10.56 ± 1.42 vs. 6.75 ± 3.62 days, $p = 0.008$) and a longer mean length of hospitalization (8.00 ± 2.08 vs. 3.58 ± 1.56 days, $p < 0.001$) than the other patients. At laboratory examination,

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patients with CCHF had statistically significant lower leukocyte and platelet counts, more prolonged coagulation parameters, and greater AST, ALT, LDH, and CK levels than the other patients. No mortality or complications occurred in the study. Both infectious causes, such as URTI, cellulitis, and brucellosis, and non-infectious causes may resemble CCHF. Although they are not pathognomonic, some indicators, including a longer symptom duration and hospitalization, cytopenia, elevated liver enzymes, creatine kinase and prolonged coagulation parameters, were found to be in favor of CCHF.

Introduction

Crimean-Congo hemorrhagic fever (CCHF) is a tick-borne, viral infection caused by Crimean-Congo hemorrhagic fever virus from the genus *Nairovirus* in the family *Bunyaviridae*. It is mainly transmitted to humans either by bites of several genera of ixodid ticks or direct contact with the blood or tissues of viremic patients or livestock [1]. It is an arboviral disease widely distributed across the world from southern Russia and the Black Sea region to southern Africa [2]. It was first recognized in Turkey in 2002, and since, Turkey has come to represent a special case in CCHF epidemiology and is an ''epicenter'' of the disease with more than 1000 confirmed cases per year [3]. People living at more than 836.5 m above sea level and working in agriculture and animal husbandry are at significant risk for CCHF especially between May and July [4]. Most cases occur in the central and eastern parts of Turkey. Erzurum and the surrounding area, where this study was performed, is endemic for CCHF [5].

Crimean-Congo hemorrhagic fever has a reported general mortality in Turkey of up to 5% [6]. The clinical course in children is milder than that in adults. The clinical spectrum may extend to an unfavorable severity including vascular leaks, multi-organ failure, shock, and hemorrhagic disease. Nevertheless, a recent serosurvey conducted in endemic regions of Turkey, including Erzurum, reported that 88% of the study population had previously experienced subclinical infections [7]. It is important to identify cases of CCHF quickly due to the risk of outbreak. Nosocomial cases have been reported [8,9]. Physicians should be alert and careful to differentiate other diseases that have epidemiological, clinical, and laboratory properties overlapping with CCHF. The purpose of this study was to emphasize the differential diagnosis of CCHF in children in an endemic country and to demonstrate differences in clinical and laboratory characteristics between CCHF and other clinical spectra.

Materials and methods

This study was carried out between April 01 and September 01, 2015 at the Erzurum Regional Training and Research Hospital, which is a referral center for the eastern part of Turkey. Patients with suspected CCHF from Erzurum, outlying districts and neighboring cities were either admitted directly or referred from other hospitals. Hospitalized children below 18 years of age and with CCHF suspected on the basis of epidemiological, clinical, and laboratory characteristics were evaluated retrospectively.

Blood samples were collected from all patients on admission, and all patients were monitored with respiratory and droplet isolation precautions until the PCR results were obtained. Real-time PCR (Qiagen® CCHFV Viral RNA Kit, Qiagen, Hilden, Germany) was carried out by the local reference laboratory. Negative PCR results were confirmed with indirect immunofluorescence assay tests. Isolation was maintained for children with CCHF until discharge. These children were closely monitored (patients with thrombocyte counts <50,000/uL were transferred to isolation rooms in the Anesthesiology Intensive Care Unit) for vital signs and clinical findings. Investigations including hemogram, C-reactive protein, liver enzymes (aspartate aminotransferase [AST], alanine aminotransferase [ALT], gamma glutamyl transferase [GGT] and lactate dehydrogenase [LDH]), creatine kinase (CK), and coagulation parameters (activated partial thromboplastin time [aPTT], prothrombin time [PT], and INR international normalized ratio [INR]) were performed from the serum samples.

Intravenous hydration with appropriate volume and electrolyte concentrations for each child was started as a standard treatment regimen. A definitive treatment plan was implemented following confirmation of diagnosis. Children with CCHF were hospitalized until fever symptoms resolved, adequate oral intake was observed, and normal thrombocyte counts and coagulation parameters

were achieved. Other patients were discharged as soon as CCHF diagnosis was excluded and other indications for hospitalization were resolved. The study was approved by the local ethical committee.

Statistical analyses were performed using SPSS for Windows version 17.0 (SPSS Inc., Chicago, IL). Compatibility of measurable variables with normal distributions was evaluated using the Kolmogorov–Smirnov test. Quantitative data were expressed as the mean ± standard deviation (SD), and qualitative data were described as numbers (%). Differences between patients diagnosed with CCHF and non-CCHF patients were compared using Fisher's exact test for dichotomous variables, the Student's t test or the Mann–Whitney *U* test for continuous variables. Significance was set at $P < 0.05$.

Results

Seventeen (81%) of the 21 patients had a history of tick bites, 2 (9.5%) had a history of contact with CCHF patients, and 2 (9.5%) had no history of exposure but were living in an endemic region. The ticks were mostly found ($n = 5$, 23.8%) in the axillary region. Other regions included the trunk ($n = 4$, 19%), arms ($n = 4$, 19%), head ($n = 2$, 9.5%), neck ($n = 1$, 4.8%), and legs ($n = 1$, 4.8%). Three patients had an underlying disorder: cerebral palsy and diabetes insipidus, epilepsy or periodic fever, aphthous stomatitis, pharyngitis, and adenitis (PFAPA) syndrome.

Nine (42.9%) patients were diagnosed with CCHF, whereas 7 (33.3%) had viral upper respiratory tract infections (URTIs), 2 patients (9.5%) had brucellosis, 1 patient (4.7%) had PFAPA syndrome episode, 1 patient (4.7%) had cerebral palsy, diabetes insipidus, acute gastroenteritis, and hypernatremic dehydration, and 1 patient (4.7%) had cellulitis following tick bite. CCHF diagnosis was made using RT-RCR. No patients were serology positive.

The mean age of the CCHF patients was 116.1 ± 53.6 months, and the mean age of the other non-CCHF patients was 94.1 ± 52.1 months ($p = 0.02$). All patients experienced fever. Other frequent symptoms were malaise, diarrhea and vomiting, and abdominal pain and none of these symptoms differed statistically significantly between the patient groups. Myalgia was observed in 3 CCHF patients but in none of the non-CCHF patients ($p = 0.03$). Three patients (2 with CCHF and 1 with URTI) had spontaneous epistaxis and a received thrombocyte suspension. Physical examination findings revealed tonsillopharyngitis in 4 patients (2 with CCHF, 2 with URTI) and petechiae in 2 patients (1 with CCHF, 1 with URTI). Although no atypical cells were observed in peripheral blood smears, bone marrow aspiration was performed due to persistence of thrombocytopenia, and malignancy was excluded in 1 patient. Three patients with URTI had cervical micro lymphadenopathy. No patients had hepatosplenomegaly.

Crimean-Congo hemorrhagic fever patients had a longer mean duration of symptoms (10.56 ± 1.42 vs. 6.75 ± 3.62 days, $p = 0.008$) and a greater mean length of hospitalization (8.00 ± 2.08 vs. 3.58 ± 1.56 days, $p < 0.001$) than the other patients. At laboratory examination, CCHF patients had statistically significant lower leukocyte and platelet values and greater AST, ALT, LDH, and CK levels than the other patients (Table 1). The CCHF patients were not given any antiviral treatment, including ribavirin. One child with CCHF was given N-acetyl cysteine therapy due to a rapid increase in liver enzymes. Prolonged bleeding parameters (aPTT, INR, or PT) were observed in 11 (52.4%) patients. These parameters were statistically higher in children with CCHF than in other children (Table 1). Fresh frozen plasma was used in 5 (23.8%) CCHF patients. One of these children was also given vitamin K supplementation. Of the other children without CCHF, 3 received antibiotic therapy and 1 received desmopressin acetate therapy. All patients in the study group were discharged without complications.

Discussion

The differential diagnosis of CCHF includes other viral hemorrhagic infections, bacterial septicemias, salmonellosis, brucellosis, rickettsiosis, leptospirosis, borreliosis, malaria, Lyme disease, brucellosis, Q fever, hepatitis viruses, febrile neutropenia, and vitamin B12 deficiency [10]. In the present study, all patients were suspected and received a preliminary diagnosis of CCHF on the basis of appropriate exposure history, symptoms, and initial laboratory findings. Accurate diagnosis is only possible after laboratory confirmation. Some patients were eventually diagnosed with different clinical spectra, such as URTI, PFAPA episode, cellulitis, and diabetes insipidus together with hypernatremic dehydration.

The mean age of the children in this study was approximately 9.5 years, which is similar to the mean age of another pediatric CCHF patient population [11]. The non-CCHF patients were younger than the CCHF patients, and most were diagnosed with a viral URTI. Definitive etiological causes were not investigated. Viral URTI infections may present with

Table 1 Clinical and laboratory evaluation of patients hospitalized due to preliminary diagnosis of Crimean-Congo hemorrhagic fever (CCHF).

	CCHF patients $n = 9$ (42.9%)	Other patients[a] $n = 12$ (57.1%)	p Value
Age (months) (mean ± SD)	116.1 ± 53.6	94.1 ± 52.1	**0.02**[*]
Duration between tick bite and start of symptoms (days) (median [min—max])	1 [1—5]	2 [1—7]	0.30
Duration of symptoms (days) (mean ± SD)	10.56 ± 1.42	6.75 ± 3.62	**0.008**[*]
Duration of hospitalization (days) (mean ± SD)	8.00 ± 2.08	3.58 ± 1.56	**<0.001**[*]
Male sex *n* (%)	8 (%88.9)	10 (%83.3)	0.70
Symptoms			
Fever, *n* (%)	9 (100%)	12 (100%)	NS
Malaise, *n* (%)	8 (88.9%)	7 (58.3%)	0.10
Diarrhea and vomiting, *n* (%)	7 (77.8%)	5 (41.7%)	0.09
Abdominal pain, *n* (%)	5 (55.6%)	3 (25.0%)	0.10
Cough, *n* (%)	4 (44.4%)	4 (33.3%)	0.60
Nasal discharge/obstruction, *n* (%)	3 (37.5%)	5 (41.7%)	0.50
Sore throat, *n* (%)	3 (33.3%)	1 (8.3%)	0.10
Myalgia, *n* (%)	3 (33.3%)	0 (0%)	**0.03**[*]
Bleeding, *n* (%)	2 (22.2%)	1 (8.3%)	0.30
Rash, *n* (%)	1 (11.1%)	1 (8.3%)	0.80
Arthralgia, *n* (%)	0 (0%)	2 (16.7%)	0.20
Laboratory findings			
Lowest WBC value (/uL) (median [min—max])	1905 [1266—4010]	5330 [1400—24,900]	**0.02**[*]
Lowest Hb value (g/dL) (mean ± SD)	13.1 ± 1.5	12.6 ± 2.0	0.40
Lowest platelet value (/uL) (median [min—max])	66,000 [17,000—1,39,900]	1,57,450 [27,480—4,39,100]	**0.02**[*]
Highest CRP level (0—5 mg/dL) (mean ± SD)	2.37 ± 2.36	2.65 ± 2.61	0.70
Highest AST level (5—34 U/L) (median [min—max])	256 [120—1138]	40.5 [16—159]	**0.001**[*]
Highest ALT level (0—55 U/L) (median [min—max])	157 [50—363]	16.5 [9—154]	**0.001**[*]
Highest GGT level (12—64 U/L) (median [min—max])	34 [15—313]	11.5 [8—84]	0.07
Highest LDH level (125—220 U/L) (median [min—max])	520 [341—1679]	352 [200—1007]	**0.05**[*]
Highest CK level (30—200 U/L) (median [min—max])	390 [109—25,312]	100 [31—1320]	**0.03**[*]
Highest aPTT level (21—35 s) (mean ± SD)	34.7 ± 11.0	25.6 ± 2.7	**0.007**[*]
Highest INR level (0.8—1.2) (mean ± SD)	1.35 ± 0.17	1.14 ± 0.10	**0.01**[*]
Highest PT level (10.5—14.9 s) (mean ± SD)	15.9 ± 2.4	13.8 ± 1.2	**0.04**[*]

[*] All bold values are statistically significant.

[a] Upper respiratory tract infections, brucellosis, PFAPA (periodic fever, aphtous stomatitis, pharyngitis, and adenitis) syndrome episode, cerebral palsy + diabetes insipidus + acute gastroenteritis + hypernatremic dehydration, cellulitis due to tick bite.

min, minimum; max, maximum; SD, standard deviation; WBC, white blood cell count; Hb, hemoglobin; CRP, C-reactive protein; AST, aspartate aminotransferase; ALT, alanine aminotransferase; GGT, gama glutamyl transferase; LDH, lactate dehydrogenase; CK, creatine kinase; aptt, activated partial thromboplastin time; INR, international normalized ratio; PT, prothrombin time.

conjunctivitis, coryza, cough, diarrhea, hoarseness, stomatitis, and viral exanthema, which all resemble CCHF [12]. The laboratory findings of these infections may also mimic CCHF. Worsening cytopenia [13,14] and prolonged PT and aPTT as well as elevated serum LDH, AST, ALT, and CK are common during the course of viral respiratory infections [15]. Even patients with URTI may exhibit spontaneous bleeding, as was observed in one thrombocytopenic patient in the current study. By virtue of their being one of the most common admission diagnoses in children, we assume that viral URTIs will continue to complicate the differential diagnosis of CCHF in endemic regions. Erzurum is also endemic for brucellosis. This may also mimic CCHF [16]. Two patients were diagnosed with brucellosis in the present study. Although brucellosis has distinct transmission routes, overlapping properties compatible with CCHF resulted in these patients being tested for CCHF. Brucellar clinical polymorphism, including fever, arthralgia, gastrointestinal symptoms, fatigue and anorexia, and laboratory characteristics, such as cytopenia, clotting disorders and elevated LDH, AST, and ALT, may also resemble CCHF [17—19]. Patients with other diagnoses were also initially considered to have a preliminary diagnosis of CCHF due to fever and other nonspecific symptoms and compatible epidemiological and laboratory data.

Crimean Congo hemorrhagic fever involves various clinical phases: incubation, pre-hemorrhagic, hemorrhagic, and convalescence periods. The incubation period usually lasts from 1 to 7 days depending on the virus titer and route of transmission [20]. In this study, the incubation period lasted between 1 and 5 days after tick bite in CCHF patients. No difference was observed between CCHF and non-CCHF patients in terms of mean incubation periods. All patients in this study had fever, which is the predominant symptom of the pre-hemorrhagic period in CCHF. Additionally, nonspecific symptoms, including malaise, vomiting, diarrhea, and abdominal pain, which were also widely seen in our patients, are common during the course of CCHF [11,21]. Tonsillopharyngitis, which has been reported as common among children with CCHF [11], was present in 2 cases of CCHF in this study, which may also lead to confusion during differential diagnosis. The hemorrhagic period usually begins between days 3 and 5 of the disease and continues for another 2—3 days [10]. Petechiae, hematomas, and bleeding from various areas may be seen. Epistaxis, which is one of the most frequent types of bleeding in pediatric subjects, was observed in 2 out of 9 (22.2%) patients in the current study [11,21]. Prolongation in coagulation parameters has previously been reported in children with CCHF and was similar in the present study [11,21].

Other laboratory findings of CCHF patients in this study, such as the low thrombocyte and leukocyte counts and high AST, ALT, LDH, and CK levels, differed significantly from those of the other patients. Leukopenia, thrombocytopenia, prolonged aPTT, elevated LDH and ALT, and the presence of melena and somnolence have previously been reported as independent predictors of mortality among CCHF patients [22,23]. Although no mortality was observed in the study population, prominent findings involving cytopenia, increased liver enzymes and CK, and prolonged bleeding parameters should raise suspicion of CCHF in endemic countries.

Tasdelen Fisgin et al. reported that two-thirds of CCHF patients were initially misdiagnosed because of nonspecific early signs and symptoms [24]. Very high subclinical infection rates have also been reported [7]. Although lower mortality has been documented in children [6,11], it is vitally important to diagnose CCHF and isolate suspected patients until diagnosis due to CCHF's major public health consequences. The majority of our study population (81%) had a history of tick bites. The Turkish Ministry of Health cites a figure of approximately 60% for CCHF patients [25].

In this study, both the total symptomatic period and the length of hospitalization were longer in CCHF patients than in the other patients. This may reflect the more serious and longer clinical course of CCHF. The mean duration of symptoms (pre-hemorrhagic and hemorrhagic) in CCHF patients was compatible with the time until convalescence [3,10]. The length of hospitalization in the CCHF patients may also reflect time required to recover from the thrombocytopenia and prolonged coagulation parameters.

Definitive diagnosis of CCHF is based on laboratory confirmation. Viral RNA is detectable in serum samples using RT-PCR until the 18th day [20]. This was the method used to diagnose CCHF patients in this study. There is no proven specific treatment for CCHF, and patients were not, therefore, given antiviral medication. As advised in the literature, the use of supportive treatment with i.v. fluids, gastric protective drugs, thrombocyte suspension and fresh frozen plasma, if necessary, has been reported [26,27].

Conclusions

Despite the small sample size, this study highlights the importance of the differential diagnosis

of CCHF. Our results reveal that not only infectious causes, such as URTI, cellulitis, and brucellosis, but also specific non-infectious causes may resemble CCHF, especially in endemic regions. Although they are not pathognomonic, some laboratory findings, including cytopenia, elevated liver enzymes, creatine kinase, and prolonged coagulation parameters, were found to be in favor of CCHF. A clinical survey of CCHF patients took longer than in other patients due to the longer duration of symptoms and hospitalization. Patients with epidemiological characteristics and clinical and laboratory data compatible with CCHF should immediately be placed in isolation and tested for CCHF. This will not only obviate unnecessary testing and medication but also prevent public health threats associated with CCHF.

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Competing interests

None declared.

Ethical approval

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