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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