Evaluation of Renal Involvement in Children with Crimean-Congo Hemorrhagic Fever

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SUMMARY: The aim of the present study was to evaluate renal involvement in children with Crimean-Congo hemorrhagic fever (CCHF). Forty-four children infected with CCHF virus and 30 controls were enrolled in the study. Urine neutrophil gelatinase-associated lipocalin (uNGAL) and urine protein levels were measured in the patient and control groups. Clinical and laboratory findings of the patient and control groups were compared. uNGAL levels were higher in the patient group than that in the control group (P < 0.001). Of the 44 patients, 26 (59.1%) were proteinuric. uNGAL levels in proteinuric patients were higher than those in non-proteinuric patients (P = 0.035). There was a positive correlation between uNGAL and urine protein levels in the patient group (R = 0.614, P < 0.001). Due to renal involvement, increased proteinuria and increased uNGAL levels were observed in children with CCHF. In these children, measuring urine total protein and uNGAL levels can be useful to monitor renal involvement due to CCHF.

INTRODUCTION

Crimean-Congo hemorrhagic fever (CCHF), which is a disease described in more than 30 countries, is a potentially fatal tick-borne acute viral infection that causes hemorrhagic symptoms (1,2). CCHF virus (CCHFV) is transmitted to humans by the bite of infected ticks; direct contact with blood or infected tissues from viremic animals, such as sheep and ostriches; and direct contact with the blood or secretions of an infected person (2,3). CCHF is commonly severe in humans and has been identified in urine samples (4).

Studies have reported mortality rates of 3–30% in patients with CCHFV infection among different countries and age groups (5). In Turkey, the Ministry of Health reported an overall fatality rate of 5% (6) for CCHF in adults and 1.35% in children. Death is typically preceded by hemorrhagic diathesis, shock, and multiorgan system failure 1–2 weeks following the onset of symptoms.

CCHF is reportedly milder among children (6). Tonsillopharyngitis, abdominal pain, diarrhea, and myalgia have been reported to be more common among children compared with adults, while hepatomegaly and splenomegaly have been reported to occur in one-third of patients (7–10). Hepatorenal insufficiency has been reported in South Africa but not in Turkey or Iran (10–12). In patients with CCHF, urinalysis may reveal proteinuria and hematuria, as well as the development of oliguria and azotemia (5,11,13). However, there is insufficient data regarding the evaluation of renal involvement in children with CCHF.

The aim of the present study was to evaluate renal involvement in children with CCHF infection through urine and blood laboratory analyses.

MATERIALS AND METHODS

Forty-four children diagnosed with CCHF who were treated at Cumhuriyet University Hospital between April 2010 and May 2011 were included in the study. The study protocol was approved by the Human Ethics Committee of the Cumhuriyet University School of Medicine.

Patients exhibiting symptoms such as fever, fatigue, headache, hypersensitivity, severe pain of the extremities and back, lack of appetite, vomiting, stomach ache, and diarrhea were suspected to have CCHF. CCHF diagnoses were confirmed by serological tests, enzyme linked-immunosorbent assay (IgM), or PCR performed by the Refik Saydam Hifzisıhha Institute (Ankara, Turkey). Blood samples were obtained from all patients during the first 7 days after the onset of symptoms (the acute phase). Serum and urine samples from the 44 patients were obtained in the acute phase, and laboratory parameters were measured. A control group consisted of 30 healthy individuals with no history of other potential health problems. Exclusion criteria were as follows: presence of systemic diseases such as chronic renal failure, diabetes mellitus, ischemic heart disease, and malignancy and history of trauma; heavy exercising; or use of drugs that potentially affects biochemical parameters.

Patient characteristic, including age, gender, history of tick bite(s), duration of symptoms, body temperature, complete blood count results, and laboratory values, such as activated partial thromboplastin time (APTT), prothrombin time (PT), international normalized ratio, D-dimer, aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase

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RESULTS

A total of 44 children with CCHF were included in the study group. Baseline characteristics of the patients with CCHF and the controls are listed in Table 1. The most commonly encountered clinical symptoms were tonsillopharyngitis, nausea, vomiting, headache, abdominal pain, diarrhea, and facial-conjunctival hyperemia. Hemorrhage was observed in only 2 patients. Urinalysis confirmed leukocyturia in 4 patients, while none had hematuria or positive urine cultures.

Urinary total protein (mean, 0.22; range, 0.07–1.0 g/dL) and uNGAL (mean, 1.96; range, 0.3–31.6 μg/L) levels in the patient group were statistically significantly higher than those in the control group (mean, 0.09; range, 0.06–0.15 g/dL and mean, 0.33; range 0.04–0.8 μg/L, respectively; both, P < 0.001).

Of the 44 children with CCHF, 26 (59.1%) were proteinuric, while 18 (40.9%) were non-proteinuric. uNGAL levels in the proteinuric group was statistically significantly higher than those in the non-proteinuric group (P < 0.035). APTT was significantly higher in the proteinuric group than that in the non-proteinuric group (P < 0.05). Other clinical and laboratory parameters (i.e., AST, ALT, LDH, CK enzyme activities, and coagulation tests) did not show any significant differences between groups (Tables 1 and 2).

In the patient group, there was a positive correlation between uNGAL and urine protein levels (R = 0.641, P < 0.001) (Fig. 1). Moreover, a negative correlation was found between uNGAL and hemoglobin (Hb) levels and platelet counts (R = –0.518, P = 0.014; R = –0.642, P < 0.001, respectively).

DISCUSSION

In the present study, we found an increase in uNGAL levels, which is a marker of acute kidney injury (AKI), in children with CCHF. Proteinuria was positive in 59.1% of the children. In proteinuric children with CCHF, the increase in uNGAL levels was higher than that in non-proteinuric children. However, there were no significant differences in eGFR, serum BUN, and creatinine levels between the groups. Moreover, AST, ALT, LDH, CK, and APTT levels in the proteinuric group were higher than those in the non-proteinuric group. In the patient group, there was a positive correlation between the uNGAL and urine protein levels, while
Table 2. Comparison of laboratory findings of the study groups

<table>
<thead>
<tr>
<th>Study marker</th>
<th>Control group (n = 44)</th>
<th>Proteinuric CCHF (n = 26)</th>
<th>Non-proteinuric CCHF (n = 18)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urine NGAL (pg/mg creat.)</td>
<td>0.33 (0.04–0.8)</td>
<td>2.08 (1.01–3.16)</td>
<td>1.06 (0.30–6.47)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Urine protein (mg/mg creat.)</td>
<td>0.09 (0.06–0.15)</td>
<td>0.37 (0.20–1.00)</td>
<td>0.15 (0.07–0.19)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td><strong>Biochemical tests</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>eGFR</td>
<td></td>
<td>104.62 (73.4–165.2)</td>
<td>99.80 (93.2–163.1)</td>
<td>0.438</td>
</tr>
<tr>
<td>BUN (mg/dL)</td>
<td>10.0 (3.0–22.0)</td>
<td>8.0 (3.0–17.0)</td>
<td>5.024</td>
<td></td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td>0.6 (0.3–0.9)</td>
<td>0.6 (0.2–1.0)</td>
<td>0.496</td>
<td></td>
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<tr>
<td>Bilirubin (mg/dL)</td>
<td>0.65 (0.1–1.0)</td>
<td>0.5 (0.3–2.2)</td>
<td>0.775</td>
<td></td>
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<tr>
<td>ALT (IU/L)</td>
<td>22 (13–93)</td>
<td>13 (9–69)</td>
<td>0.017*</td>
<td></td>
</tr>
<tr>
<td>AST (IU/L)</td>
<td>51 (25–252)</td>
<td>26 (18–109)</td>
<td>0.012*</td>
<td></td>
</tr>
<tr>
<td>LDH (IU/L)</td>
<td>295 (199–729)</td>
<td>205 (128–369)</td>
<td>0.023*</td>
<td></td>
</tr>
<tr>
<td>CK (IU/L)</td>
<td>224 (79–18765)</td>
<td>86 (39–412)</td>
<td>0.019*</td>
<td></td>
</tr>
<tr>
<td>CRP (mg/dL)</td>
<td>14.9 (1.0–14.3)</td>
<td>5.0 (1.2–61.3)</td>
<td>0.443</td>
<td></td>
</tr>
<tr>
<td>Fibrinogen (mg/dL)</td>
<td>239 (136–280)</td>
<td>252 (238–303)</td>
<td>0.099</td>
<td></td>
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<tr>
<td><strong>Coagulation tests</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prothrombin time(s)</td>
<td>15.1 (9.7–23.0)</td>
<td>12.0 (11.4–19.5)</td>
<td>0.116</td>
<td></td>
</tr>
<tr>
<td>APTT(s)</td>
<td>44.4 (16.0–65.1)</td>
<td>35.0 (23.8–41.9)</td>
<td>0.021*</td>
<td></td>
</tr>
<tr>
<td>INR</td>
<td>1.36 (0.89–2.05)</td>
<td>1.09 (1.03–1.74)</td>
<td>0.141</td>
<td></td>
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<tr>
<td>D-dimer (∗10⁵)</td>
<td>1.35 (0.11–39.18)</td>
<td>1.14 (0.20–5.10)</td>
<td>0.311</td>
<td></td>
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<tr>
<td><strong>Complete blood count</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leukocyte (∗10⁹ cells/L)</td>
<td>2.7 (1.4–4.3)</td>
<td>2.5 (1.5–4.7)</td>
<td>0.713</td>
<td></td>
</tr>
<tr>
<td>Hemoglobin (g/dL)</td>
<td>13.5 (11.7–14.5)</td>
<td>14.3 (12.3–15.8)</td>
<td>0.116</td>
<td></td>
</tr>
<tr>
<td>Thrombocyte count (∗10⁹ cells/L)</td>
<td>98 (28–203)</td>
<td>126 (69–158)</td>
<td>0.193</td>
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</tbody>
</table>

*P < 0.05, significance.
NGAL, neutrophil gelatinase-associated lipocalin; eGFR, estimated glomerular filtration rate; BUN, blood urea nitrogen; ALT, alanine aminotransferase; AST, aspartate aminotransferase; LDH, lactate dehydrogenase; CK, creatine kinase; CRP; C-reactive protein; APTT, activated partial thromboplastin time; INR, international normalized ratio.

In CCHF, the most commonly observed laboratory findings are anemia, leukopenia, thrombocytopenia, increased AST/ALT levels, prolonged bleeding time, PT, and APTT, elevated fibrin degradation products, and decreased fibrinogen levels. Proteinuria and hematuria can be observed in urinalysis, and patients may develop oliguria and azotemia (11). Previous studies have reported acute renal failure due to viral infections, such as influenza A virus infection (17). Swanepoel et al. (18) reported early stage proteinuria and hematuria and increased creatinine levels accompanied by increased BUN levels in children with CCHFV infections.

A previous study by Ergönlü et al. (8) reported no case of renal failure in 35 CCHF patients. During routine follow-up in children with CCHF, creatinine and urine protein (by strip test) levels and the presence of leukocytes and erythrocytes (by microscopy) were evaluated; however, the strip test was not sufficiently sensitive to evaluate proteinuria. The development of hematuria and leukocyturia due to CCHF is rare in children. In our study, 59.1% of the children had proteinuria during the period of active infection, but none of the patients had hematuria, while leukocyturia was present in 2. Moreover, we did not observe any increase in serum BUN or creatinine levels in the proteinuric group. Hence, measuring quantitative urine protein levels following renal involvement during the active phase in

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**Fig. 1.** Evaluation of the relation between urine NGAL levels and urine protein levels in children with CCHF (R = 0.614; P < 0.001).

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the correlation between platelet count and Hb levels was negative.

CCHF has a milder course in children compared with adults. Moreover, the mortality rate is lower in children (6). Tonsillopharyngitis, abdominal pain, diarrhea, and myalgia have been reported to be the most common symptoms in children (5, 7, 9). In our study, the most commonly observed clinical symptoms were tonsillopharyngitis, nausea, vomiting, headache, abdominal pain, diarrhea, and facial-conjunctival hyperemia.

In CCHF, the most commonly observed laboratory findings are anemia, leukopenia, thrombocytopenia, increased AST/ALT levels, prolonged bleeding time, PT, and APTT, elevated fibrin degradation products, and decreased fibrinogen levels. Proteinuria and hematuria can be observed in urinalysis, and patients may develop oliguria and azotemia (11). Previous studies have reported acute renal failure due to viral infections, such as influenza A virus infection (17). Swanepoel et al. (18) reported early stage proteinuria and hematuria and increased creatinine levels accompanied by increased BUN levels in children with CCHFV infections.

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children with CCHF can be useful.

Proteinuria during the active infection phase in our study could be related to many factors such as AKI because uNGAL levels, an early and sensitive marker of AKI, were increased in children with CCHF. Moreover, the increase in uNGAL levels was correlated with urine protein levels. In CCHF, renal injury may develop due to direct viral renal damage or renal hypovolemia caused by sepsis or disseminated intravascular coagulation. Thrombotic microangiopathy with acute renal failure has been reported in CCHF (19), suggesting that renal injury may develop as a result of thrombotic microangiopathy. NGAL is a protein synthesized in the distal nephrons of the kidney and secreted into the urine by the thick ascending limb of the loop of Henle and the collecting ducts of the kidney (20,21). Previous studies have reported a correlation between increased uNGAL levels and severity of renal damage in various systemic diseases (22,23). We found that uNGAL levels in children were positively correlated with AST, ALT, LDH, and CK levels, and APTT, while there was a negative correlation between serum Hb levels and platelet counts. Urine protein and uNGAL levels were higher in severe cases. These findings suggested that severity of disease can accelerate the development of renal injury.

Most children with transient proteinuria diagnosed at screening urinalysis do not have kidney disease (24). Proteinuria in children with CCHF can be transient due to fever, stress, or systemic infection, whereas the increase in uNGAL levels, which is an early and sensitive marker for AKI, is due to the renal injury (22,23). Therefore, the measurement of uNGAL levels can be used in the differential diagnosis of proteinuria in these patients.

The presence of proteinuria during the active phase of infection in children with CCHF and an increase in uNGAL levels due to the severity of the disease suggested that AKI can develop in these patients. We believe that quantitative measurement of urine protein and uNGAL (a marker of AKI) may be useful in the evaluation of renal status during follow-up examinations.

The limitations of the present study included the limited number of patients and the inability to evaluate the correlation between renal involvement and mortality because there were no fatal cases. We believe that cohort studies with larger patient populations including fatal cases are needed to elucidate these correlations.

**Conflict of interest** None to declare.

**REFERENCES**


