Intestinal protein loss in patients with haemorrhagic fever with renal syndrome

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Abstract

Background. In haemorrhagic fever with renal syndrome (HFRS) vascular dysfunction has been observed in various organs, but the involvement of the intestine has not yet been reported. This study was performed to evaluate the association of intestinal protein loss in this disease with other clinical parameters reflecting vascular permeability or disease severity.

Methods. Twenty patients with HFRS were included in this study. Intestinal protein loss was measured by \[^{99mTc}\text{human serum albumin}\] (\[^{99mTc}\text{HSA}\]) scintigraphy in the acute stage, and quantitative analysis of protein loss was measured by the faecal clearance of alpha 1-antitrypsin (C\(_{\text{AT}}\)) in the acute and the recovery stages. C\(_{\text{AT}}\) was then compared with clinical parameters reflecting disease activity and vascular permeability.

Results. \[^{99mTc}\text{HSA}\] scintigraphy was positive in 13 (65%) patients, and C\(_{\text{AT}}\) in the acute stage was significantly increased as compared with C\(_{\text{AT}}\) in the recovery stage (40.5 ± 24.1 vs 9.2 ± 4.2 ml/day, \(<0.001\)). C\(_{\text{AT}}\) was associated with serum albumin levels, frequency of hypotensive episodes, severity of acute renal failure, and degree of thrombocytopenia.

Conclusions. Our data suggest that the increased vascular permeability of HFRS is associated with the increased intestinal loss of plasma proteins, which might represent one of the parameters of disease severity in HFRS.

Keywords: haemorrhagic fever; renal syndrome; hypoalbuminaemia; intestinal tract

Introduction

Haemorrhagic fever with renal syndrome (HFRS) is an acute inflammatory disease caused by Hantavirus [1–4] and characterized by vascular dysfunction [5–8]. Clinically, retroperitoneal oedema and free fluid accumulations in the body cavities with haemoconcentration reflect the vascular leak present in HFRS. Evidence of the vascular leak is frequently observed in patients dying of hypotensive shock [7,8]. This vascular leak may be associated with low serum protein values [7,8].

Protein loss via the intestinal tract has been well documented in diseases associated with vasculitis, such as systemic lupus erythaematosus and mixed connective tissue disease, and is explained by increased vascular permeability due to intestinal vasculitis [9,10]. Since increased vascular permeability is present in HFRS, increased protein loss via the intestinal tract is possible. We evaluated the intestinal protein loss in HFRS. First, we confirmed intestinal protein loss by abdominal scintigraphy using technetium-99m-labelled human serum albumin (\[^{99mTc}\text{HSA}\]) and faecal clearance of alpha\(_{1}\)-antitrypsin (C\(_{\text{AT}}\)) [11–14]. Secondly, we compared the intestinal protein loss with clinical parameters representing the disease severity.

Methods

Patient population

Twenty patients with HFRS were included in this study. The diagnosis of HFRS was based on clinical manifestations (high fever, back pain, acute renal failure, proteinuria or haematuria, and thrombocytopenia) and indirect immunofluorescence antibody test against the Hantavirus. Fifteen patients were male and five were female. The mean age was 35 ± 8 years (range 20–52 years). None of the subjects had a medical history of protein-losing enteropathy, such as inflammatory bowel disease.

Measurement of clinical and laboratory parameters

The association of the intestinal protein loss with clinical parameters (hypotension, pleural effusion, haemodialysis treatment) was also investigated. Blood pressure was measured with manometer; hypotension was defined as
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<90/60 mmHg. Pleural effusion was diagnosed by chest X-ray.

On admission, blood samples were obtained for complete blood count, creatinine, albumin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), and lactate dehydrogenase (LDH), and a 24-h urine was collected for protein measurement. Acute renal failure was defined as serum creatinine \( > 2.0 \) mg/dl. Leukocytosis was defined as leukocyte count \( > 10,000/\text{mm}^3 \), thrombocytopenia as platelet count \( < 100,000/\text{mm}^3 \), and hypoalbuminaemia as serum albumin level \( < 3.5 \) g/dl.

Haemodialysis was performed in cases of severe pulmonary oedema, in oliguric or anuric states, and in cases of severe azotaemia (serum creatinine \( > 10 \) mg/dl or blood urea nitrogen \( > 100 \) mg/dl).

Results of \(^{99m}\text{Tc-HSA\ scan}\)

No radionuclide uptake by the thyroid was observed within 24 h. Thirteen patients (65%) had evidence of radioactive tracer moving down the intestinal tract, demonstrating protein loss into the intestinal lumen. Radioactivity was frequently observed in the right colon, but infrequently in the transverse and the left colon. Figure 1 shows scintigraphic findings 24 h after the intravenous injection of \(^{99m}\text{Tc-HSA}\), with positive (Figure 1a) and negative (Figure 1b) results.

Comparison of clinical factors between normal and increased \( C_{\text{AT}} \) groups

Hypotension developed in seven patients (53.8%) with increased \( C_{\text{AT}} \), but there were no episodes of hypotension in patients with normal \( C_{\text{AT}} \) (\( P = 0.016 \)). The incidence of pleural effusion in the increased \( C_{\text{AT}} \) group tended to be higher than in the normal \( C_{\text{AT}} \) group, but there was no statistical difference between these two groups (46.1 % vs 14.2%, \( P = 0.154 \)). Haemodialysis treatment was needed in 10 patients (76.9%) from the increased \( C_{\text{AT}} \) group and in only two patients (28.6%) from the normal \( C_{\text{AT}} \) group (\( P = 0.035 \)). The lowest level of serum albumin in the group with increased \( C_{\text{AT}} \) was significantly lower than that in the group with normal \( C_{\text{AT}} \) (2.8 ± 0.1 vs 3.4 ± 0.2 g/dl, \( P = 0.001 \)). The platelet count was lower in the patients with increased \( C_{\text{AT}} \), as compared to that in the patients with normal \( C_{\text{AT}} \) (27,000 ± 22,700 vs 76,000 ± 80,000/mm\(^3\), \( P = 0.049 \)). Haemoglobin (17.3 ± 2.4 vs 14.9 ± 1.5 g/dl, \( P = 0.032 \)) and serum ALT (119 ± 96 vs 53 ± 23 IU/L, \( P = 0.032 \)) were significantly lower in patients with increased \( C_{\text{AT}} \) than in those with normal \( C_{\text{AT}} \).
increased in the increased $C_{AT}$ group, as compared with those in the normal $C_{AT}$ group (Table 3).

**Correlation of the serum albumin level with $C_{AT}$**

There was a significant negative correlation between the lowest level of serum albumin during admission and $C_{AT}$ ($r = -0.554$, $P = 0.011$), but there was no correlation between the lowest level of serum albumin and the amount of proteinuria on admission ($r = 0.062$, $p = 0.638$).

**Discussion**

Our study clearly demonstrates that protein loss via the intestinal tract occurs in the acute stage of HFRS. The intestinal protein loss, demonstrated by $^{99m}$Tc-HSA scintigraphy and $C_{AT}$ levels showed a significant increase in the acute stage, and follow-up $C_{AT}$ in the recovery stage returned to the normal range. To our knowledge, this is the first report demonstrating that protein loss via the intestinal tract is increased in HFRS.

To evaluate the association of intestinal protein loss with increased vascular permeability in HFRS, we compared the $C_{AT}$ with other clinical parameters (hypotension, pleural effusion, haemoconcentration, thrombocytopenia). It is well known that hypotension, pleural effusion, and haemoconcentration are the parameters of increased vascular permeability in HFRS [7,8]. Potential mechanisms of thrombocytopenia include immune pathways leading to vascular endothelial injury and intravascular coagulation. Therefore, the degree of thrombocytopenia has been suggested as a clinical parameter of increased vascular permeability due to vascular dysfunction [7]. In this study, higher incidences of hypotension, pleural effusion, and haemoconcentration were associated with increased $C_{AT}$. The degree of thrombocytopenia was also associated with increased $C_{AT}$. These findings all suggest that intestinal protein loss is one of the results of increased vascular permeability in HFRS.

Our study was extended to determine whether intestinal protein loss represented the disease severity of HFRS. Serum albumin level, LDH, and the degree of renal failure have all been suggested as parameters of the disease severity in HFRS [7,8]. Haemodialysis treatment was needed in 80% of the patients with increased $C_{AT}$, while only two (28.5%) with normal $C_{AT}$ underwent haemodialysis. Patients with increased $C_{AT}$ showed significantly low serum albumin levels, as compared with those with normal $C_{AT}$. In addition, there was a good correlation between $C_{AT}$ and serum albumin level. The LDH levels also tended to be higher in the increased $C_{AT}$ group than in the normal $C_{AT}$ group. These findings together suggest that intestinal protein loss is closely associated with the disease severity of HFRS.

In general, hypoalbuminaemia can be attributed to the conditions of decreased synthesis (deficient protein intake, liver disease), excessive protein loss, or increased catabolism [15]. In HFRS, hypoalbuminaemia is frequently observed in the acute stage of HFRS [4], and its mechanism seems to be multifactorial, e.g., increased catabolism of protein, proteinuria, poor oral intake, and hepatic dysfunction. Therefore, it is difficult to define the exact cause of hypoalbuminaemia. However, the high correlation between intestinal protein loss and serum albumin level suggests that the intestinal protein loss partly contributed to hypoalbuminaemia. Further studies are needed to define other factors leading to hypoalbuminaemia.

In general, increased intestinal protein loss could be associated with increased water loss (such as diarrhoea) via the intestinal tracts in the acute stage of HFRS, abdominal pain, nausea, and vomiting are frequently observed, but diarrhoea is rarely observed [2,4,16]. In this study, diarrhoea was observed in only one patient (5%). Furthermore, some patients needed magnesium hydroxide to induce defecation. Therefore, it is less likely that episodes of diarrhoea have any significant impact on intestinal protein loss.

In this study, we demonstrated the intestinal protein loss in HFRS, but its actual pathophysiological mechanism remains unknown. Potential mediators, which increase vascular permeability during the acute stage of HFRS, are tumor necrosis factor (TNF)-alpha, interleukin 1 and 2, and nitric oxide [5,7]. Green et al. [17] reported that the level of TNF-alpha was related to the degree of pleural effusion, representing the increased vascular permeability in patients with dengue haemorrhagic fever. Therefore, it can be postulated
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Fig. 2. Comparison of $\text{C_AT}$ among patients with increased $\text{C_AT}$ during the acute and recovery stages. $\text{C_AT}$ in the recovery stage was measured when serum albumin level was normalized ($\geq 3.5 \text{ g/dl}$). $\text{C_AT}$ in the recovery stage was significantly decreased, as compared with that in the acute stage ($9.2 \pm 4.2 \text{ vs } 40.5 \pm 24.1 \text{ ml/day, } P < 0.001$).

Table 2. The results of $\text{C_AT}$ and HSA scintigraphy

<table>
<thead>
<tr>
<th>$\text{C_AT}$</th>
<th>HSA scintigraphy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Negative</td>
</tr>
<tr>
<td>Normal</td>
<td>6</td>
</tr>
<tr>
<td>High</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>7</td>
</tr>
</tbody>
</table>

Table 3. Comparison of clinical parameters between normal and increased $\text{C_AT}$ groups

<table>
<thead>
<tr>
<th>Clinical parameters</th>
<th>Normal $\text{C_AT}$ ($n=7$)</th>
<th>Increased $\text{C_AT}$ ($n=13$)</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Platelets (×10^3)</td>
<td>$76,000 \pm 80,000$</td>
<td>$27,000 \pm 22,000$</td>
<td>0.049</td>
</tr>
<tr>
<td>Haemoglobin (g/dl)</td>
<td>$14.9 \pm 1.5$</td>
<td>$17.3 \pm 2.4$</td>
<td>0.032</td>
</tr>
<tr>
<td>Haematocrit (%)</td>
<td>$45.0 \pm 5.5$</td>
<td>$50.5 \pm 7.1$</td>
<td>0.096</td>
</tr>
<tr>
<td>Albumin* (g/dl)</td>
<td>$3.4 \pm 0.2$</td>
<td>$2.8 \pm 0.1$</td>
<td>0.001</td>
</tr>
<tr>
<td>AST (IU/l)</td>
<td>$108.2 \pm 62.1$</td>
<td>$226.2 \pm 196.6$</td>
<td>0.144</td>
</tr>
<tr>
<td>ALT (IU/l)</td>
<td>$52.8 \pm 23.0$</td>
<td>$119.2 \pm 95.9$</td>
<td>0.032</td>
</tr>
<tr>
<td>LDH (IU/ml)</td>
<td>$692.1 \pm 271.3$</td>
<td>$1217.5 \pm 740.1$</td>
<td>0.091</td>
</tr>
</tbody>
</table>

Values are mean±SD.

*Lowest level during admission.

that the vascular injury and the subsequent increased production of the aforementioned cytokines may be responsible for the intestinal protein loss in HFRS.

$^{99m}$Tc-HSA scintigraphy has been utilized as a screening test for the intestinal protein loss because of its non-invasive and simple technique [13,14,18]. In addition, $^{99m}$Tc-HSA is highly stable in vivo, and thus the radioactivity found in the intestines directly signifies the intestinal loss of $^{99m}$Tc-HSA. The AT (molecular weight: 50 000 Da) is also useful in detecting intestinal protein loss [12,19,20]. The results of the $^{99m}$Tc-HSA scintigraphy and the $\text{C_AT}$ levels were in concordance in our study: $^{99m}$Tc-HSA scan and $\text{C_AT}$ were both positive in 12 out of the 20 patients, both negative in

* Preliminary results were presented at the 36th European Renal Association-European Dialysis and Transplant Association congress (Madrid, Spain) in 1999.
six patients. These two studies were in discordance in only two patients (Table 2). To exclude false-positive results, patients with gastrointestinal haemorrhage and inflammatory bowel disease were excluded from this study. Non-uptake of free technetium in the thyroid gland was used as a guide for excluding misinterpretation of the scintigraphic imaging results.

In conclusion, our study demonstrates that intestinal loss of plasma proteins is frequently observed in patients with HFRS and that it is closely associated with the clinical parameters reflecting increased vascular permeability and disease severity of HFRS.

References


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