Hypertransaminasemia in children with viral gastroenteritis

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We investigated the rates of increase in serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels of patients with rotavirus, norovirus and enteric adenovirus gastroenteritis. Two hundred children with viral gastroenteritis were evaluated for hypertransaminasemia retrospectively. The patients were between 0 - 17 years (mean ± SD: 5.10 ± 3.01) of age. ALT was elevated up to 67 IU/L in 7 (8.5%) patients in the rotavirus group (n=82), whereas it was elevated in 3 (4.0%) and 1 (2.3%) patients in the norovirus (n=74) and adenovirus (n=44) groups, respectively. AST was elevated up to 89 IU/L in 20 (24.4%) patients in the rotavirus group, whereas it was elevated in 6 (8.1%) and 1 (2.3%) patients in the norovirus and adenovirus groups, respectively. Both transaminases were elevated in 7.3%, 1.4%, and 2.3% of patients in the rotavirus, norovirus, and adenovirus groups, respectively. The increases in ALT and AST levels were found to be significantly higher in the rotavirus group (n=27) than in the norovirus (n=9), and adenovirus group (n=2) (p<0.05). Mean serum ALT and AST levels in the rotavirus group were significantly higher than those in the norovirus and adenovirus group (p<0.05). Our study investigated the correlation between viral gastroenteritis and hypertransaminasemia. When evaluating a patient with hypertransaminasemia physicians should remember to consider acute gastroenteritis due to some viruses as a cause of elevated AST and ALT.

Keywords: acute gastroenteritis, enteric adenovirus, hypertransaminasemia, norovirus, rotavirus.

Introduction

Rotavirus, norovirus, enteric adenoviruses are commonly encountered agents of viral gastroenteritis. Rotavirus is the major cause of acute gastroenteritis in children under 5 years of age worldwide. This virus causes 114 million childhood gastroenteritis episodes per year [1]. Besides gastroenteritis and dehydration, rotavirus may also cause hepatitis, nephritis, pneumonia, exanthema, disseminated intravascular coagulation, haemophagocytic lymphohistiocytosis, and neurological complications such as encephalitis, cerebellitis, and convulsions [2-9]. Some authors reported the increased levels of transaminases in some cases with rotavirus gastroenteritis [10-14]. Norovirus (NoV), a member of the calicivirus family, is known to be a pathogen that causes acute gastroenteritis in patients of all ages. It was firstly reported as the agent of the epidemic in Norwalk, Ohio, in 1968 [15-19]. In recent studies, NoV was recognized as the major infectious agent attributed to outbreaks and sporadic cases of infectious gastroenteritis especially after the rotavirus vaccination became widespread [20-22]. With the increasing popularity of rotavirus vaccines, the incidence of rotavirus infection in patients hospitalized with diarrhea is estimated to be decreased, and the relative importance of norovirus infection is gradually rising. Central nervous system manifestations such as status epilepticus and encephalopathy were reported in cases with NoV in recent studies [23, 24]. However, other possible
complications of NoV infection that may influence the other organs are still not known exhaustively.

Adenoviruses are double-stranded non-enveloped DNA viruses. There are 51 different serotypes, but only serotypes 40 and 41, and less frequently serotype 31 may cause acute gastroenteritis [25]. The incidence of enteric adenovirus infections in children is reported to be between 3.1% and 13.5% in studies performed in Europe, Asia, Northern and Southern America [25-30].

Hypertransaminasaemia is remarkable finding in the dehydrated children. It has been reported in acute viral gastroenteritis, especially rotavirus. There has so far been some report of the hypertransaminasaemia accompanied by norovirus infection in the past. Hypertransaminasaemia has not been reported by adenovirus infection. The present report includes pediatric patients with hypertransaminasaemia accompanied by gastroenteritis due to rotavirus, norovirus, and adenovirus. We primarily purposed to investigate of the rates of increase in serum AST and ALT levels of patients with rotavirus, norovirus and enteric adenovirus gastroenteritis as well as to compare the levels between these groups.

**PATIENTS AND METHODS**

**Study population**

Two hundred children who were admitted to the Department of Paediatrics, between January 2010 and January 2013 with acute gastroenteritis, and diagnosed as viral (adenovirus, norovirus, and rotavirus) gastroenteritis were included in this study. The patients' data were retrieved retrospectively from the hospital records. Exclusion criteria were as follows; the presence of any agent that may have caused the acute gastroenteritis other than these viruses (adenovirus, norovirus, and rotavirus), presence of chronic liver disease or chronic drug use, and positive history of the administration of hepatotoxic drugs (paracetamol, antibiotics, etc.) prior to presenting clinical situation due to acute gastroenteritis.

**Data collection**

Rapid antigen tests and PCR for adenovirus, norovirus, and rotavirus were used to detect aetiological agents. Venous blood samples were collected into Vacuette tubes (Greiner Bio-One, Monroe, NC). Tubes were kept on the roller for 10 minutes. Then, a complete blood count (CBC) was studied within 30 minutes after the blood samples were drawn. Haemoglobin, haemotocrit, white blood cell (WBC), platelets and mean platelet volume (MPV) values were evaluated according to CBC results of the patients.

The levels of AST and ALT were measured in serum specimens with the photometric method (Roche Diagnostics, Integra 800, Mannheim, Germany). C-reactive protein (CRP) was measured in serum specimens with the nephelometric method (Beckman Coulter Diagnostics, Image 8000, Brea, CA, USA). Cut off levels of transaminases were used as suggested as in the Nelson Textbook of Pediatrics, 19th edition [31].

**Statistical analysis**

Statistical analysis was performed by using SPSS 21.0 statistical program software. Conformity to the normal distribution of data was assessed by Kolmogorov-Smirnov test. Descriptive statistics for continuous variables as mean ± standard deviation were shown as frequencies and percentages for categorical variables. Analysis of the differences between categorical variables, chi-square test was performed inside. More than two groups corresponding to the normal distribution instead of the variables were compared by ANOVA test or Welch test for pairwise comparisons by the Tukey test, or a Dunnett’s three t test was used instead. More than two groups do not conform to the normal distribution of variables in comparison Kruskal-Wallis test, therefore the Mann-Whitney U test for pairwise comparisons were made. P <0.05 was considered a statistically significant difference in the case. Conformity to the normal distribution of data was assessed by Kolmogorov-Smirnov test.

**RESULTS**

A total of 200 children were enrolled in this study. There were 112 (56.0%) males and 88 (44.0%) females with a male/female ratio of 1.27 to 1. The patients were between 0-17 years of age (mean ±SD: 5.10±3.01). The maximum AST and ALT levels in the three gastroenteritis groups were as follows: rotavirus, norovirus, and adenovirus.
Rotavirus, norovirus, adenovirus agents were detected in 82 (41.0%), 74 (37.0%) and 44 (22.0%) patients, respectively (Table 1).

Increased ALT values were detected in 8.5%, 4.0%, and 2.3% of the patients with rotavirus, norovirus, and adenovirus, respectively (Table 1). Increased AST values were detected in 24.4%, 8.1%, and 2.3% of the patients with rotavirus, norovirus, and adenovirus, respectively (Table 1). The increase in AST and ALT levels was found to be statistically significant in the rotavirus gastroenteritis group when compared with adenovirus and norovirus gastroenteritis groups (both p <0.05). Elevated levels in both ALT and AST were detected in six patients (7.3%), one patient (1.4%), and one patient (2.3%) in the rotavirus, norovirus, and adenovirus group, respectively (p=0.132 (Table 1).

The abnormal levels of transaminases in this report indicated that the levels of ALT and AST were elevated up to 67 IU/L and 89 IU/L, respectively. Mean serum ALT and AST levels in the rotavirus group were significantly higher than those in the norovirus and adenovirus group (AST 44.3±13.67, 36.5±9.27 and 38.7±8.57 respectively, p<0.05; ALT 27.2±12.63, 22.5±9.91 and, 19.6±9.32 respectively, p<0.05). Mean haemoglobin levels, haematocrit levels, mean WBC count, platelet count, MPV

Table 1 - Demographical features and transaminases levels of patients with rotavirus, norovirus, and adenovirus.

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Mean ± SD</th>
<th>Rotavirus (No.=82)</th>
<th>Norovirus (No.=74)</th>
<th>Adenovirus (No.=44)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
<td>-Male</td>
<td>-Female</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>43 (52.4)</td>
<td>39 (52.7)</td>
<td>30 (68.2)</td>
<td>0.183</td>
</tr>
<tr>
<td>Ast (Mean ± SD)</td>
<td>43.56 ± 13.74</td>
<td>36.4 ± 9.24</td>
<td>38.04 ± 8.04</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>Alt (Mean ± SD)</td>
<td>27.2 ± 12.62</td>
<td>22.1 ± 9.63</td>
<td>19.2 ± 8.73</td>
<td>0.000</td>
<td></td>
</tr>
<tr>
<td>Elevated ALT (n, %)</td>
<td>7 (8.5)</td>
<td>3 (4.0)</td>
<td>1 (2.3)</td>
<td>0.268</td>
<td></td>
</tr>
<tr>
<td>Elevated AST (n, %)</td>
<td>20 (24.4)</td>
<td>6 (8.1)</td>
<td>1 (2.3)</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>Elevated both ALT and AST (No., %)</td>
<td>6 (7.3)</td>
<td>1 (1.4)</td>
<td>1 (2.3)</td>
<td>0.132</td>
<td></td>
</tr>
</tbody>
</table>

Table 2 - Comparison of laboratory findings of the study population (mean ± SD).

| Haemoglobin (g/dL) | 12.64±1.10 | 12.8±1.02 | 12.3±1.03 | 0.037   |
| Haemotocrit (%)    | 36.39±2.79 | 36.9±2.82 | 35.0±2.75 | 0.003   |
| WBC (count/mm³)    | 11032±4690 | 13510±5275 | 11490±4847 | 0.006   |
| Platelets (count/mm³) | 318390±97282 | 358406±103356 | 305695±83911 | 0.007   |
| MPV (fL)           | 9.2±0.75 | 9.14±0.73 | 9.2±0.62 | 0.576   |
| CRP (mg/L)         | 11.2±18.9 | 9.7±19.6 | 16.2±24.06 | 0.099   |
| Alt (IU/L)         | 27.2±12.62 | 22.1±9.63 | 19.2±8.73 | 0.000   |
| Ast (IU/L)         | 43.56±13.74 | 36.4±9.24 | 38.04±8.04 | 0.001   |

Table 3 - Hospitalization rates and the degree of dehydration of patients based on factors.

<table>
<thead>
<tr>
<th>Hospitalization (No., %)</th>
<th>Rotavirus (No.=82)</th>
<th>Norovirus (No.=74)</th>
<th>Adenovirus (No.=44)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Observed follow-up (No., %)</td>
<td>41 (50%)</td>
<td>40 (54.1%)</td>
<td>19 (43.2%)</td>
<td>0.521</td>
</tr>
<tr>
<td>Mild dehydration (No., %)</td>
<td>17 (20.7%)</td>
<td>23 (31.1%)</td>
<td>13 (29.5%)</td>
<td>0.390</td>
</tr>
<tr>
<td>Moderate dehydration (No., %)</td>
<td>55 (67.1%)</td>
<td>46 (62.2%)</td>
<td>26 (59.1%)</td>
<td>0.521</td>
</tr>
<tr>
<td>Severe dehydration (No., %)</td>
<td>10 (12.2%)</td>
<td>5 (6.8%)</td>
<td>5 (11.4%)</td>
<td>0.521</td>
</tr>
</tbody>
</table>
value, and serum CRP levels were similar in the three groups (p >0.05) (Table 2). Among 200 patients with gastroenteritis, 100 of them were (50%) hospitalized, and 100 (50%) were treated with intravenous fluids in the daycare unit. Fifty-three patients (26.5%) had mild dehydration, 127 patients (63.5%) had moderate dehydration and 20 (10%) patients had severe dehydration. There was no statistically significant difference between the three groups when comparing the need of hospitalization and dehydration degrees (p > 0.05) (Table 3).

**DISCUSSION**

AST is an enzyme found primarily in the liver, heart, kidney, pancreas, and muscles. This enzyme is normally elevated in tissue damage including the liver, heart, muscles, pancreas, and kidney. In contrast, ALT is an enzyme that appears in liver cells, and in lesser amounts in the kidneys, heart, and skeletal muscles, which means that it is a relatively specific indicator of acute liver cell damage [12].

Rotavirus gastroenteritis is recognized to be associated with intestinal epithelial involvement as well as systemic findings including the liver [11]. In this study, we showed that besides rotavirus gastroenteritis, norovirus and adenovirus gastroenteritis also have liver manifestations. We found increase in ALT levels in 8.5% and in AST levels in 24.4% of the patients with rotavirus gastroenteritis.

In a study of 35 under-2-years-old infants hospitalized for gastroenteritis due to rotavirus and vomiting and dehydration, Kovacs et al. found an increase in ALT levels in 72% of the patients and an increase in AST levels in 60% of the patients [14]. Recently, Kawashima et al. in their study on a total of 26 children with convulsion-positive (n=15) and convulsion-negative (n=11) rotavirus gastroenteritis, reported an increase in ALT levels in 11.5% and an increase in AST levels in 88.5% of the patients [12]. The study of Teitelbaum et al. is the most comprehensive in this field [13]. In their study, 75 rotavirus gastroenteritis patients were examined, and an increase in both ALT and AST levels was found in 20% of the patients and an increase in AST levels alone in 71% of the patients [13]. Grimwood et al. assessed only AST levels in their study of 39 children with acute rotavirus gastroenteritis and found an increased level of AST in 8 (21%) of the patients [32]. Chiappini et al. reported that 8 (57%) of the 14 children hospitalized with rotavirus gastroenteritis had ALT elevation [33].

There has so far been no report of the elevation of the levels of transaminases accompanied by norovirus infection in the past. We found increase in ALT levels in 4.0% and in AST levels in 8.1% of the patients with norovirus gastroenteritis. Tsuge et al. experienced 4 pediatric cases with an elevation of the serum transaminase levels accompanied by norovirus gastroenteritis [34]. Zende et al. found norovirus gastroenteritis in a 56-year-old woman, accompanied by marked elevation of transaminase [35]. There was no increase in ALT and AST with adenovirus gastroenteritis in the literature. However, we found increased ALT levels in 2.8% and increased AST levels in 2.8% of the patients with adenovirus gastroenteritis. Antigenemia may occur in norovirus, rotavirus, and adenovirus infections. More studies concerning the mechanism of the elevation of transaminases due to norovirus and adenovirus are thus called for in the future.

**CONCLUSION**

In conclusion, our study investigated the correlation between rotavirus gastroenteritis and transaminase elevation. Our results clearly signify a liver influence in rotavirus infections. Therefore, rotavirus infections should be kept in mind when evaluating the aetiology of transaminase elevation in patients with acute gastroenteritis. Transaminase levels were increased in patients with rotavirus and norovirus, as well as adenovirus. Increased transaminase levels in adenovirus gastroenteritis were detected in our study, which was a difference from literature. When evaluating a patient with hypertransaminasaemia physicians should remember to consider acute gastroenteritis due to some viruses as a cause of elevated AST and ALT. Hypertransaminasaemia may be seen secondary to viral infection or dehydration. One must remember that AST and ALT levels measured in the serum can be arbitrarily high, for instance due to medications and some patients with dehydration.
Conflict of interest statement: On behalf of all authors, the corresponding author states that there is no conflict of interest.

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Ethical approval: This study was ethically approved by the local ethical committee of Yeditepe University Hospital (date: 02.06.2009).

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REFERENCES


