Gastroenteritis-Associated Hyperamylasemia

Prevalence and Clinical Significance

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Background: Serum amylase levels can be elevated in various pathological conditions. However, acute gastroenteritis has not been widely recognized as a cause for hyperamylasemia.

Patients and Methods: We conducted a retrospective study of amylase results for all patients hospitalized or discharged from the emergency department with a diagnosis of gastroenteritis from April through November 1999. Patients with other possible medical causes for elevated amylase levels were excluded. We also compared the clinical and laboratory parameters of hyperamylasemic vs normoamylasemic hospitalized patients with gastroenteritis.

Results: A total of 1041 patients with acute gastroenteritis were identified. Serum amylase levels were determined in 701 patients and were abnormally elevated in 66 of them. In 15 patients, other possible causes of hyperamylasemia were present, and these patients were excluded. The mean serum amylase level among the remaining 51 patients (7.4% of the remaining 686 patients with gastroenteritis) was 1.32 of the upper normal level, with a range of up to 2.2 times the upper normal range. Clinicians tended to admit more hyperamylasemic patients than normoamylasemic patients (10 of 51 vs 65 of 635; \( P = .03 \), 1 sided). However, the course of gastroenteritis in the hospitalized hyperamylasemic patients did not differ significantly from that in the hospitalized normoamylasemic patients, as judged by the clinical signs and symptoms, laboratory results, length of hospital stay, and need for antibiotics.

Conclusions: Gastroenteritis is associated with a mild to moderate elevation of serum amylase levels in a significant portion of patients and should be included in the differential diagnosis of hyperamylasemia. Such elevation, however, does not seem to bear clinical significance in terms of the severity of disease.

Arch Intern Med. 2002;162:689-692

ELEVATED SERUM amylase levels have long been recognized as a useful marker for pancreatic inflammation. There are several other clinical conditions in which hyperamylasemia is present, however, such as salivary gland disorders, gastrointestinal perforation or infarction, renal failure, and macroamylasemia. Although gastroenteritis is not widely considered as a cause of hyperamylasemia, several reports have documented elevated amylase levels in patients with gastroenteritis of specific pathogenesis. However, to our knowledge, the prevalence of hyperamylasemia among nonselected patients with acute gastroenteritis and the impact of elevated serum amylase levels on disease course have not been hitherto studied.

RESULTS

A total of 1041 patients were seen in the emergency department with a diagnosis of acute gastroenteritis from April 1999 through November 1999. Amylase results were available for 701 (67.0%) of these patients. Sixty-six patients (9.4%) had elevated amylase values. Fifteen patients were excluded after the application of the exclusion criteria previously described, leaving 51 patients (7.4%) with gastroenteritis-related elevated amylase levels out of 686 patients with gastroenteritis and available amylase results. The average amylase level among the hyperamylasemic patients was 396 IU/L (×1.32 of upper normal level), with a range of 319 to 657 IU/L (up to ×2.2 of upper normal value). Amylase values were available for 13 of the 51 patients within 1 month of current hospital referral, and were normal in all of them. The lipase value was available for only 1 patient with hyperamylasemia, and was elevated as well.

Overall, 75 (10.9%) of the 686 patients with gastroenteritis who were seen at the emergency department were
PATIENTS AND METHODS

Patients with any abdominal complaint who come to the emergency department in our medical center usually have their blood drawn for a “surgical routine,” which includes determination of amylase levels. We retrospectively examined amylase values in all patients who were discharged from the emergency department or who were admitted to the hospital with a diagnosis of gastroenteritis during 8 months in 1999 (April-November). Amylase values were determined in all patients by the 2-point rate test using slide spectrophotometry (Vitros300; Johnson & Johnson, Raritan, NJ) with a wavelength of 540 nm. Patients with elevated amylase values were further evaluated. The normal range of amylase levels in our laboratory is 30 to 300 IU/L, determined as the range of 2 SD of the mean, thereby allowing for 2.5% of above-normal results in the reference population.1 In our study, patients were considered to have hyperamylasemia only when their amylase values were higher than 318 IU/L, which is the value at 3 SD of the normal population. By choosing this higher cutoff point, we limited the expected incidental results above this value to only 1% of reference population.1 Patients with a known pancreatic abnormality (such as chronic pancreatitis or pancreatic tumor), patients with known risk factors for pancreatitis (such as alcohol abuse or ingestion of potential pancreatic-cytotoxic drugs), patients with renal failure, and patients with salivary gland disorders were also excluded, as were patients with hemolytic blood samples and patients with a known biliary tract disease or elevated direct bilirubin levels. A single patient with celiac disease was also excluded, because several case reports indicate the occurrence of hyperamylasemia in this disease.2 We then compared epidemiological, clinical, and laboratory parameters of the hospitalized patients who had gastroenteritis and hyperamylasemia with those who had normal amylase values. We also reviewed the files of all patients who were admitted during the study period with an emergency department provisional diagnosis of acute pancreatitis to see if this diagnosis was altered to gastroenteritis at discharge. Statistical analysis was performed by $\chi^2$ test with Yates correction or by t test, as appropriate.

hospitalized. There was a significant tendency to admit more patients with gastroenteritis and elevated amylase levels (10/51, 19%), compared with patients with normal amylase values (65/635, 10.2%; $P = .03$, 1-sided). Hyperamylasemic patients did not differ significantly in their age and sex from normoamylasemic patients (Table). Several parameters were examined to find out whether the clinical course of gastroenteritis differed between patients with normal and elevated amylase levels (Table). No difference was found in reported subjective symptoms of abdominal pain, vomiting, and diarrhea or in the type of stool reported (watery vs mucous or bloody). The percentage of patients with temperatures above 37.8°C was also similar in the 2 groups. No difference was found in the laboratory parameters studied, which included the presence of leukocytosis (white blood cell count, >11000/mm³ [$>11.0 \times 10^9/L$]), electrolyte abnormalities, and determination of albumin levels, as well as elevated urea levels, reflecting the degree of dehydration. Stool culture results were available for 26 of the 75 hospitalized patients; 23 of the 26 stool samples were collected from normoamylasemic patients. Two of these 23 cultures were positive for organisms (1 for Shigella flexneri, and 1 for Shigella species); however, the numbers are too small for statistic analysis. The length of hospital stay, the percentage of patients treated with antibiotics, and the percentage of patients who underwent abdominal x-ray examination were similar in the 2 groups. The results of the abdominal x-ray examination, which were interpreted as either normal or as revealing nonspecific dilation of small-bowel loops, were also similar in both groups (data not shown). In addition, we identified 84 patients who were admitted during the study period with an emergency department diagnosis of acute pancreatitis. In 14 of the 84 patients, the evaluation during hospitalization yielded different diagnoses, such as biliary colic or other gastrointestinal disorders. In none of the patients was the diagnosis changed to gastroenteritis at discharge.

Amylase is found in several tissues, most notably the pancreas and the salivary glands. The finding of elevated serum amylase levels most commonly reflects pancreatic inflammation or injury. However, hyperamylasemia can result from several other acute abdominal events, such as intestinal perforation, ischemia, or infarction. Other well-recognized causes of elevated serum amylase levels include salivary gland disorders; tumors such as ovarian and lung carcinomas; renal failure, which causes reduced amylase clearance; and macroamylasemia.3 In most of these conditions, the amylase level is only moderately elevated.4 Whether the level of hyperamylasemia can be relied on to differentiate between pancreatitis and other disorders has been a matter of controversy. In general, however, when the clinical circumstances are suggestive of pancreatitis, a cutoff point of more than 3 times the upper normal amylase value has been shown to be highly specific for pancreatic inflammation.5,6 Measurement of lipase levels, pancreatic isoenzymes of amylase, and urine excretion of amylase are additional biochemical aids to diagnosis.3 Gastroenteritis is generally not considered a cause of hyperamylasemia and is not mentioned in the differential diagnosis of hyperamylasemia in standard gastroenterological or surgical textbooks.6,7 Our study shows for the first time, to our knowledge, that a substantial number (about 7.4% in our series) of patients with gastroenteritis have a mild to moderate increase in serum amylase levels. In all 13 patients who were examined within a month after the gastroenteritis episode, amylase levels were found to be normal, showing the temporal association between gastroenteritis and hyperamylasemia. The fact that amylase values in our series did not exceed 2.2 times the upper normal value should be interpreted cautiously, as inclu-
sion of patients in this retrospective study was based on emergency department diagnosis of acute gastroenteritis. Thus, it could be assumed that some patients with gastroenteritis and higher amylase levels were not diagnosed by the emergency department physician as having acute gastroenteritis but rather as having suspected pancreatitis, and were therefore not included in this study population. However, such misrepresentation is unlikely in light of our finding that in none of the 84 patients admitted during the study period with suspected pancreatitis was the diagnosis changed to gastroenteritis at discharge.

The pathogenesis of hyperamylasemia in our patients is not clear. One possible cause of elevated amylase values in these patients is direct involvement of the pancreas in the infectious inflammatory process that affected the intestine. There are several reports suggesting pancreatic damage during infectious gastroenteritis. In a prospective study of 188 patients with Campylobacter jejuni enteritis, Pitkanen et al. reported a rate of 6% of complicating pancreatitis as determined by elevation of amylase and lipase levels. However, lipase levels were not measured in all patients; the degree of elevated amylase levels at which pancreatitis was diagnosed was not specified; and imaging studies were not reported to have been performed. In another prospective study of 47 patients with Salmonella enteritis, 62% of patients were diagnosed as having concurrent pancreatitis based on elevated amylase and lipase levels. However, in a prospective study of 147 cases of acute gastroenteritis, in which Salmonella was the causative agent in 51 patients and Campylobacter in 22, there were no cases of pancreatitis. Mild elevation of amylase levels was found in only 4 patients, 1 with Salmonella and none with Campylobacter. These conflicting results have led to a dispute regarding the incidence of pancreatitis in infectious gastroenteritis. Only a few case reports adequately document the concomitant occurrence of pancreatitis with infectious gastroenteritis through detailed clinical course and an elevation of amylase and/or lipase levels of more than 3 times the normal values, along with imaging studies. Altogether, only 4 patients have been so described: 2 with Campylobacter enteritis, 1 with typhoid, and 2 with rotavirus. While the postulated mechanism is direct invasion of pancreatic parenchyma by the pathogen, no proof by direct tissue visualization or cultivation of pathogen has been available so far.

An alternative mechanism to explain the elevated amylase levels in patients with gastroenteritis was offered by some investigators based on the long-observed barrier dysfunction of the intestinal mucosa during infectious diarrhea, as well as in other inflammatory diseases of the gut, a state referred to as leaky gut. Gnadinger et al described 2 patients with Salmonella enteritis and elevated amylase and lipase levels, without ultrasonographic evidence of pancreatitis. Increased intestinal permeability for chromium 51–labeled EDTA was demonstrated in both patients. The authors concluded that rather than “true” pancreatitis, mucosal inflammation causes increased permeability, or a state of leaky gut, which in turn causes increased reabsorption of pancreatic enzymes from the intestinal lumen into the blood stream. It is therefore possible that the elevated amylase levels in our patients reflect increased lumen amylase absorption through an inflamed and defective mucosal barrier, rather than direct pancreatic involvement by the inflammatory process.

The course of gastroenteritis as manifested by duration of hospital stay, need for antibiotics, and clinical symptoms and laboratory results was similar in patients with elevated or normal amylase levels in our study. This similarity in the clinical course is consistent with the findings of a previous small-scale retrospective study of elevated pancreatic enzyme levels in patients with gastroenteritis. Our study revealed that the hospitalization rate was almost twice as high among patients with gastroenteritis and hyperamylasemia (10/51, 19%) than among

### Table: Clinical and Laboratory Features of Hyperamylasemic vs Normoamylasemic Patients With Gastroenteritis

<table>
<thead>
<tr>
<th>Feature</th>
<th>Hyperamylasemic*</th>
<th>Normoamylasemic*</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rate of hospitalization†</td>
<td>10/51 (19.6)</td>
<td>65/635 (10.2)</td>
<td>.03</td>
</tr>
<tr>
<td>Hospital stay, mean ± SD, d</td>
<td>4 ± 6.74 (range, 1-23)</td>
<td>2.4 ± 2.57 (range, 1-16)</td>
<td>.48</td>
</tr>
<tr>
<td>Average age, mean ± SD, y</td>
<td>44.4 ± 23.2</td>
<td>53.8 ± 24.1</td>
<td>.26</td>
</tr>
<tr>
<td>Female patients</td>
<td>7/10 (70.0)</td>
<td>36/82 (58.0)</td>
<td>.73</td>
</tr>
<tr>
<td>Fever (&gt;37.8°C)</td>
<td>2/10 (20.0)</td>
<td>27/81 (44.0)</td>
<td>.18</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>7/10 (70.0)</td>
<td>38/59 (64.4)</td>
<td>&gt;.99</td>
</tr>
<tr>
<td>Vomiting</td>
<td>8/10 (80.0)</td>
<td>44/59 (74.5)</td>
<td>&gt;.99</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>10/10 (100.0)</td>
<td>50/59 (85.0)</td>
<td>.34</td>
</tr>
<tr>
<td>Mucus or blood in stool</td>
<td>1/8 (12.5)</td>
<td>5/29 (17.2)</td>
<td>&gt;.99</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>3/10 (30.0)</td>
<td>9/61 (14.7)</td>
<td>.36</td>
</tr>
<tr>
<td>Hyponatremia</td>
<td>1/10 (10.0)</td>
<td>3/61 (4.9)</td>
<td>&gt;.99</td>
</tr>
<tr>
<td>Elevated white blood cell count</td>
<td>5/10 (50.0)</td>
<td>29/60 (48.3)</td>
<td>&gt;.99</td>
</tr>
<tr>
<td>Elevated urea level</td>
<td>2/10 (20.0)</td>
<td>13/59 (22.0)</td>
<td>&gt;.99</td>
</tr>
<tr>
<td>Hypoalbuminemia</td>
<td>3/8 (37.5)</td>
<td>20/41 (48.7)</td>
<td>.84</td>
</tr>
<tr>
<td>Abdominal x-ray examination</td>
<td>7/10 (70.0)</td>
<td>22/59 (37.3)</td>
<td>.11</td>
</tr>
<tr>
<td>Antibiotic therapy</td>
<td>4/10 (40.0)</td>
<td>24/59 (40.6)</td>
<td>&gt;.99</td>
</tr>
</tbody>
</table>

*Values are given as number (percentage) unless indicated otherwise.
†Includes all patients with gastroenteritis seen at the emergency department.
patients with gastroenteritis and normal amylase levels (65/635, 10.2%; P = .03, 1-sided), probably owing to clinicians’ concern over the elevated amylase values. However, the similarity in the clinical course of gastroenteritis in normoamylasemic and hyperamylasemic patients argues against the need for hospitalizing patients with gastroenteritis and mild to moderate elevations of serum amylase levels, unless indicated by other clinical parameters.

Finally, one should recognize the limitation of our study, which is based on a retrospective analysis. A controlled prospective study, which will preferably include serum lipase measurement and appropriate imaging studies for all patients, is required to confirm our findings.

**CONCLUSIONS**

Gastroenteritis should be included in the differential diagnosis of mild to moderate hyperamylasemia. The pathogenesis of this hyperamylasemia is not clear, but may result either from pancreatic involvement in the inflammatory process or from increased absorption of pancreatic enzymes from the gut lumen owing to increased permeability of the intestinal mucosa. The clinical course of patients with gastroenteritis and mild to moderate hyperamylasemia does not differ significantly from that of normoamylasemic patients.

Accepted for publication July 30, 2001.

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**REFERENCES**