Serum pancreatic enzymes and imaging in paediatric acute pancreatitis: Does lipase diagnostic superiority justify eliminating amylase testing?

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Abstract

Background: In acute pancreatitis (AP), serum amylase, lipase and imaging help establish a diagnosis with recognised lipase superiority. Recent literature has debated serum amylase testing and proposed its elimination, but little is known about the diagnostic role of simultaneously measured serum amylase levels in patients with non-diagnostic lipase. This study examined the contribution of pancreatic enzymes and imaging and the role of simultaneously measured serum amylase in children with non-diagnostic serum lipase.

Methods: Retrospective medical records review of children aged <18 years with a verified discharge diagnosis of first-attack AP between January 01, 1994, and December 31, 2016.

Results: First-attack AP was confirmed in 127 children (median age, 12.5 years). The sensitivity was 90.4%, 54.3%, 42.2% and 36.4% for lipase, amylase, contrast-enhanced computed tomography and ultrasonography (US), respectively. Combination US and lipase identified 96.6% of AP cases. Simultaneous amylase and lipase measurements in 125 children showed that either was ≥3× the upper limit of normal (ULN) in 95.2%, while both were <3× the ULN in 4.8% of cases. Nondiagnostic lipase was seen in 12 (9.6%) children, and diagnosis was based on amylase level ≥3× the ULN in six children and imaging in the other six.

Conclusions: Serum amylase, serum lipase and imaging should continue for the conclusive diagnosis of AP in children. Simultaneous serum amylase measurement helped diagnose AP with non-diagnostic lipase.

Keywords: Acute pancreatitis, amylase, lipase, non-diagnostic, simultaneous, supplemental

INTRODUCTION

Serum amylase, lipase and imaging are performed to fulfil the acute pancreatitis (AP) diagnostic criteria.[1-5] With the superior sensitivity and specificity of serum lipase, the need to measure both enzymes is debated, and the elimination of amylase testing has been proposed.[7,18] Nonetheless, AP presenting with non-diagnostic serum lipase has been reported while little is known about the diagnostic role of the simultaneous measurement of serum amylase in such a scenario.[18] This study aimed to examine the contribution...
of pancreatic enzymes and imaging in the diagnosis of first-attack AP in children and explore the diagnostic value of simultaneously measured serum amylase in children presenting with non-diagnostic serum lipase.

**METHODS**

The Johns Hopkins Aramco Healthcare Health Information Unit database was searched for all discharges between January 01, 1994, and December 31, 2016, with a diagnosis of pancreatitis (acute, recurrent or chronic) using International Classification of Diseases 9th and 10th edition coding. We included children younger than 18 years. The medical records were reviewed to verify the diagnosis of AP, recurrent pancreatitis and chronic pancreatitis, in compliance with the accepted diagnostic criteria. AP was diagnosed if a patient had two of the following three criteria: abdominal pain, serum amylase, lipase ≥3× the upper limit of normal (ULN) or imaging findings suggestive of pancreatitis (enlarged pancreas, oedema, heterogeneous parenchyma, peripancreatic fluid collection). Patients who did not meet the diagnostic criteria were excluded. The date of the first-attack AP was verified, and if necessary, adjusted to accurately reflect the true date for patients who had their first attack prior to the index hospitalisation. Serum amylase and lipase measurements were simultaneously obtained within 24 h of hospitalization.

Data collected at the first-attack AP (excluding repeat attacks and chronic pancreatitis) included age, sex, total serum amylase and lipase levels, and imaging modality performed. Patients were divided into three groups (≤1 × ULN, >1 but <3× ULN and ≥3× ULN) based on the degree of pancreatic enzyme elevation and two groups (positive vs. negative for pancreatitis) based on imaging findings. Cross-tabulation of the aggregated groups was performed to study the agreement between the two serum enzymes and between the serum enzymes and the imaging modality. To study the impact of evolving laboratory and imaging technology on diagnostic outcomes, the study period was arbitrarily divided into two equal periods: period 1 (January 01, 1994 – June 30, 2005) and period 2 (July 01, 2005 – December 31, 2016).

**Statistical analysis**

Data were analysed using the Statistical Package for Social Studies (SPSS 21; IBM Corp., New York, NY, USA). The Chi-square test was used for categorical variables expressed as percentages (amylase, lipase and imaging subgroups). Age at the first-attack AP is expressed as mean, median and interquartile ratio. P value <0.05 and 95% confidence intervals were considered statistically significant.

**Ethical considerations**

This retrospective descriptive study was approved by the Institutional Review Board (IRB #18-20).

**RESULTS**

The health information unit electronic search identified 147 cases; of them, 20 were excluded because they did not meet the AP diagnostic criteria. The first-attack AP diagnosis was verified in 127 children aged 0–18 years, which constituted the study cohort.

Table 1 summarises the patient demographics, symptoms, number of children for whom serum amylase and lipase were tested, imaging modality performed and aetiology of pancreatitis. The median age at presentation was 12.5 years; and 56.7% were male. Abdominal pain was present in 113 of 118 (95.8%) children and vomiting in 87 of 119 (73.1%) children presenting with first-attack AP.

Table 2 shows the sensitivity of total serum amylase and lipase, and imaging, single and in combination, in the 127 children with first-attack AP. The sensitivity was 90.4%, 54.3%, 42.2% and 36.4% for lipase, amylase, contrast-enhanced computed tomography (CECT) and
ultrasonography (US), respectively. A combination of US and serum lipase in 117 children identified 113 (96.6%) cases while adding US to simultaneously measure amylase and lipase identified all 117 cases. Specificity and other measures of test performance (positive and negative predictive value, likelihood ratios and receiver operating characteristic curve) could not be generated as all included children were confirmed cases of AP.

Table 3 demonstrates the results of the simultaneous measurement of amylase and lipase levels in 125 children. Either of the two enzymes was ≥3× the ULN in 119 (95.2%) cases, both enzymes were ≥3× the ULN in 62 (49.6%) cases, and the two enzymes were <3× the ULN in six (4.8%) cases. Nondiagnostic serum lipase was observed in 12 of 125 (9.6%) children; in six (50%) of them, the diagnosis was based on a serum amylase level ≥3× the ULN, and the other six (50%) were identified on imaging.

Table 4 shows the agreement of imaging (suggestive of pancreatitis) to serum pancreatic enzyme levels in 123 children with first-attack AP. Among the 64 children with an amylase level ≥3× the ULN, imaging suggestive of pancreatitis was seen in 22 (34.4%) and 12 of 26 (46.2%) cases for US and CECT, respectively. Similarly, in 106 children with a lipase level ≥3× the ULN, imaging suggestive of pancreatitis was seen in 35 of 106 (33.0%) and 15 of 37 (40.5%) cases for US and CECT, respectively. Of the children with levels of both enzymes ≥3× the ULN, findings suggestive of pancreatitis were seen in 34.5% on US and in 50% on CECT.

Table 5 displays the frequency of positive imaging and diagnostic serum enzymes across the two periods in the 127 children with first-attack AP. The frequency of a negative imaging study for pancreatitis was 51.2% and 53.7% for periods 1 and 2, respectively. The frequencies of lipase test levels <3× ULN were 18.6% and 4.9% (P = 0.013), while those for amylase <3× ULN were 33.3% and 53.4% (P = 0.039) for periods 1 and 2, respectively.

Table 6 summarises the clinical, laboratory and imaging findings at first-attack AP, and the number of recurrent attacks during follow-up in six children presenting with an amylase level ≥3× the ULN and a lipase level <3× the ULN.

**DISCUSSION**

In this retrospective study, we reported the contribution of pancreatic enzymes and imaging, single or in combination, to the diagnosis of first-attack AP in 127 children. Furthermore, we explored the diagnostic value of simultaneously measured serum amylase as a supplemental test in children with...
first-attack AP presenting with a serum lipase level $<3\times$ the ULN. We then highlighted several observations.

The sensitivity of serum amylase and lipase measurements was 69 of 127 (54.3%) and 113 of 125 (90.4%) cases, respectively. Our findings are in line with previously published figures in the paediatric literature showing the superiority of lipase over amylase. The reported diagnostic accuracy of serum amylase and lipase ranged from 25% to 86% and 73% to 100%, respectively.\[26-32\] This wide variation could be due to many factors, such as the gold standard against which the enzymes were compared, the enzyme cut-off level used, the interval between symptom onset and blood collection, the presence of alcoholic pancreatitis or hypertriglyceridemia, renal failure and macro-amylasemia.\[3,33-33\] However, some of these factors are less likely to occur in children. In our cohort, the US sensitivity of 36.4% was slightly higher than the 27% reported by Coffey et al.\[31\] but lower than the 52% reported by Orkin et al.\[32\] Other studies reported a wide range of positive imaging findings for AP that ranged between 24% and 86% and between 34% and 100% for US and CECT, respectively.\[27,29,36-39\] This difference could be attributed to several reasons, such as patients’ heterogeneity of AP clinical severity, timing of imaging performed (early versus late) from symptom onset, inter-observer variability and AP imaging diagnostic criteria used.

Simultaneous serum lipase and amylase testing had better diagnostic accuracy and identified 119 of 125 (95.2%) of our cases compared to 113 of 125 (90.4%) cases for lipase-only testing. Orkin et al.\[32\] reported normal lipase in 9.6% of children with first-attack AP, with none having elevated amylase levels. However, amylase measurements were taken for only 76% of the cohort. Coffey et al.\[31\] studied children with acute and acute recurrent pancreatitis episodes, for whom amylase was measured in 78%. Those authors reported that lipase levels were $<3\times$ the ULN in 7%, while isolated amylase elevation was diagnosed in 2% of the pancreatitis episodes. However, the authors concluded that the combination of lipase and amylase provided a similar yield to that of lipase alone. The literature continues to debate performing lipase-only testing or simultaneous lipase and amylase testing in patients with suspected AP. Most of these studies examined amylase as an alternative to rather than a supplemental test for lipase. Few studies have shown no added diagnostic value of serum amylase over lipase-only testing and questioned the need for co-ordering amylase.\[14,16-18\] On the other hand, there are several reports of either normal or $<3\times$ ULN lipase levels in patients with radiologically confirmed AP, with little known about the value of simultaneously measured amylase.\[19-23,40\] In our cohort, 6 of 125 (4.8%) patients were diagnosed with elevated amylase levels. Despite the known low sensitivity, serum amylase was helpful as a supplemental test and identified a subset of AP patients presenting with non-diagnostic serum lipase levels.

There was no consistent agreement between serum enzyme levels and AP imaging findings. Among the 123 patients for whom both enzymes were measured and an imaging modality was performed, US and CECT findings suggestive of pancreatitis were seen in one-third

### Table 5: The frequency of positive imaging and diagnostic serum enzymes across two periods in 127 children with first-attack AP

| Imaging* performed in 123 children | Period 1 (January 1994 - June 2005) | Period 2 (July 2005 - December 2016) | P |
|-----------------------------------|-------------------------------------|-------------------------------------|---|
| Positive for pancreatitis         | 20 (48.8)                          | 38 (46.3)                          | 0.798 |
| Negative for pancreatitis         | 21 (51.2)                          | 44 (53.7)                          |   |
| Serum lipase measured in 125 children |                                   |                                     |   |
| Lipase $<3\times$ ULN             | 8 (18.6)                           | 4 (4.9)                            | 0.013 |
| Lipase $\geq 3\times$ ULN          | 35 (81.4)                          | 78 (95.1)                          |   |
| Serum Amylase measured in 127 children |                                   |                                     |   |
| Amylase $<3\times$ ULN             | 15 (33.3)                          | 43 (52.4)                          | 0.039 |
| Amylase $\geq 3\times$ ULN         | 30 (66.7)                          | 39 (47.6)                          |   |

*Ultrasound and/or contrast‑enhanced CT, ULN=upper limit of normal.

### Table 6: Clinical, laboratory and imaging findings at first-attack AP, and the number of recurrent attacks during follow-up in six children presenting with an amylase level $\geq 3\times$ ULN and a lipase level $<3\times$ULN

| Sex | Age (years) | Abdominal pain (days) | Vomiting | Abdominal tenderness | Imaging* pancreas | Follow-up (years) | Recurrent attacks |
|-----|-------------|-----------------------|----------|----------------------|-------------------|-------------------|------------------|
| F   | 8.6         | 4                     | Yes      | Yes                  | US and CT: normal | 4.9               | 3                |
| M   | 9.2         | 1/2                   | Yes      | Yes                  | US and CT: Normal | 5.8               | 0                |
| F   | 9.6         | 7                     | Yes      | No                   | CT: bulky         | 15.6              | 2                |
| M   | 11.3        | 1                     | Yes      | Yes                  | US: heterogeneous | 4.6               | 2                |
| F   | 14.6        | 1                     | No       | Yes                  | US and CT: normal | 18.2              | 2                |
| M   | 17.4        | 1/2                   | Yes      | Yes                  | US: bulky         | 1.7               | 0                |

ULN = Upper limit of normal. *Ultrasound and/or contrast‑enhanced CT
to one-half with serum amylase and/or lipase levels <3× the ULN; conversely, normal imaging findings were reported in two-thirds of children with amylase and/or lipase levels ≥3× the ULN. However, the diagnosis of AP was based solely on US in 4.8% of our cases in which levels of both serum enzymes were below the diagnostic threshold. The lack of correlation between serum enzyme levels and AP imaging findings is consistent with findings of previous reports.[31,37,38]

Our study has several limitations. The study population was biased towards patients with serum lipase elevation ≥3× the ULN to satisfy the AP diagnostic criteria. Therefore, patients with abdominal pain and a serum lipase level <3× the ULN, who are potential AP cases, were under-represented in our cohort. We did not account for the timing between symptom onset and performance of pancreas imaging, which may have contributed to false-negative imaging findings if performed early or late in relation to symptom onset. Additionally, changes in imaging quality and techniques over the 23-year study period could have partially contributed to the relatively low rate of positive imaging findings in our cohort. However, there was no significant difference in the rate of positive imaging across periods 1 and 2, making this limitation likely insignificant in our cohort.

CONCLUSIONS

Neither serum pancreatic enzymes measurement nor pancreatic imaging is 100% sensitive for diagnosing children with AP. However, when performed simultaneously, they complement each other and may identify a proportion of patients who would otherwise have been missed. Children with abdominal pain and a non-diagnostic serum lipase elevation <3× the ULN for whom serum amylase measurements or imaging was not performed are potentially missed cases of AP. Further studies focusing on this subset of patients are needed to explore the diagnostic value of simultaneous serum amylase as a supplemental rather than alternative test to lipase.

We conclude that simultaneous measurement of serum amylase and lipase enzymes along with an imaging modality should be considered the standard for the conclusive diagnosis of AP in children. Eliminating serum amylase measurements, as suggested in recent adult literature, may not be applicable to children undergoing testing for AP. Collecting both serum amylase and lipase at presentation and performing reflex amylase testing, if the lipase level is <3× the ULN, can be an attractive option for improving diagnostic accuracy at minimal cost.

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Conflicts of interest
There are no conflicts of interest.

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