



Patients with non-diagnostic hyperamylasaemia must be investigated and managed as per acute pancreatitis

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DECLARATIONS

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Summary

Objectives The identification of hyperamylasaemia insufficient to confidently diagnose acute pancreatitis in patients with epigastric pain poses a clinical dilemma. The aim of this study was to identify a cohort of such patients and review their presentation, investigation and outcome.

Design Patients admitted through the emergency surgical intake during a 12-month period with serum amylase levels of 100–400 IU/L were identified and case notes reviewed to confirm those presenting with upper abdominal pain. Subsequent radiological and biochemical investigations were recorded.

Participants A total of 25 patients with non-diagnostic hyperamylasaemia.

Setting Ward patients in a University Hospital.

Main outcome measures Amylase level, eventual diagnosis, drug history.

Results Twenty-five patients were identified with a mean age of 46.7 years. The median serum amylase level was 230 IU/L (range 102–358 IU/L). Twenty-two patients underwent transabdominal ultrasound at presentation, with gallstones identified in nine cases. The remaining three had documented gallstones and were awaiting elective cholecystectomy. Of the 13 patients with no evidence of cholelithiasis, six were taking medications known to cause pancreatitis, seven patients underwent computed tomography (CT) scans that identified chronic pancreatitis in three, and were non-diagnostic in four cases. These four patients underwent endoscopic ultrasound (EUS) evaluation of the biliary tree identifying microlithiasis in one but no pathology in the remaining three cases.

Conclusions Patients with hyperamylasaemia not diagnostic of pancreatitis should be carefully investigated, as gallstones will be identified in at least 50%. An accurate drug history is also invaluable.

Introduction

Acute pancreatitis is defined as an acute inflammatory process of the pancreas with variable involvement of regional tissues, or remote organ systems, associated with raised pancreatic enzymes levels in the blood or urine.¹ There is no agreement in the literature as to the exact serum amylase level required for a diagnosis of acute pancreatitis. Bollen *et al.* evaluated the definitions of acute pancreatitis in 148 studies, all of which concluded that a diagnosis of pancreatitis should include a characteristic clinical history of abdominal pain and elevated pancreatic enzyme levels.² However, the enzyme levels required to complement the clinical history ranged from 2–5 times the upper limit of normal. The guidelines currently used for the management of acute pancreatitis in the United Kingdom recommend a threshold of four times the upper limit of normal, which equates to 400 IU/L.³ While the British Society of Gastroenterology (BSG) guidelines do state that patients with lesser degrees of elevation in serum amylase and abdominal pain should be investigated as per acute pancreatitis, on a practical level, this is not widely appreciated and hence the guidelines not always followed.

Identification of hyperamylasaemia insufficient to afford a diagnosis of acute pancreatitis, poses a clinical dilemma. Is this acute pancreatitis that has presented very early or possibly late in the course of the disease thus missing the diagnostic peak, or is there another cause for the hyperamylasaemia? It is imperative to obtain an accurate history as to the onset, duration, severity and nature of the pain so as to determine whether the patient is likely to be suffering from acute pancreatitis. It is clearly necessary to determine whether there is a history of gallstone disease or of significant alcohol consumption, as these represent the commonest aetiologies of acute pancreatitis. It is also important to consider medications that may induce pancreatic injury and also family histories of acute pancreatitis.

If the history is not consistent with acute pancreatitis, then a number of differential diagnoses must also be considered, all of which have associated abdominal signs and symptoms (Table 1).⁴

The aim of this study was to identify a cohort of patients with hyperamylasaemia together with

Table 1

Potential aetiologies for hyperamylasaemia

<i>Pancreaticobiliary</i>	Acute pancreatitis Cholelithiasis Chronic pancreatitis Pancreatic trauma Post-ERCP Postoperative
<i>Abdominal conditions</i>	Appendicitis Gastroenteritis Inflammatory bowel disease Intestinal obstruction Mesenteric ischaemia Peptic ulcer disease Perforated viscera Postoperative Radiation Ruptured aortic aneurysm Trauma
<i>Female reproductive tract</i>	Ectopic pregnancy
<i>Metabolic clearance</i>	Ovarian cysts Salpingitis Cirrhosis Hepatitis Renal failure
<i>Miscellaneous</i>	Anorexia nervosa Burns Cerebral trauma Ectopic production by malignancies Ketoacidosis Salivary gland disease

appropriate clinical features and to determine the aetiology of their elevated amylase.

Materials and Methods

All patients admitted on the surgical emergency intake during a 12-month period with a hyperamylasaemia of 101–400 IU/L (normal range <100 IU/L) were identified from the biochemistry department database.

The case-notes of all patients were reviewed, and those with a history of upper abdominal pain were identified and selected as a cohort for further study. Individuals with hyperamylasaemia but no abdominal pain, and those with lower abdominal pain were excluded, as were

patients who had an elevated serum amylase in association with clinically apparent peritonitis.

The interval between onset and presentation of pain was evaluated, and the severity and evolution of pain were recorded. A detailed assessment of patient medication history was also made and all drugs known to cause acute pancreatitis were identified by cross-referencing against the British National Formulary.

The results of all subsequent radiological and biochemical investigations were obtained from the relevant clinical data systems, and patient management as well as follow-up were determined from the case-notes.

All patients were followed for a period of 5 years following their presentation with hyperamylasaemia.

Results

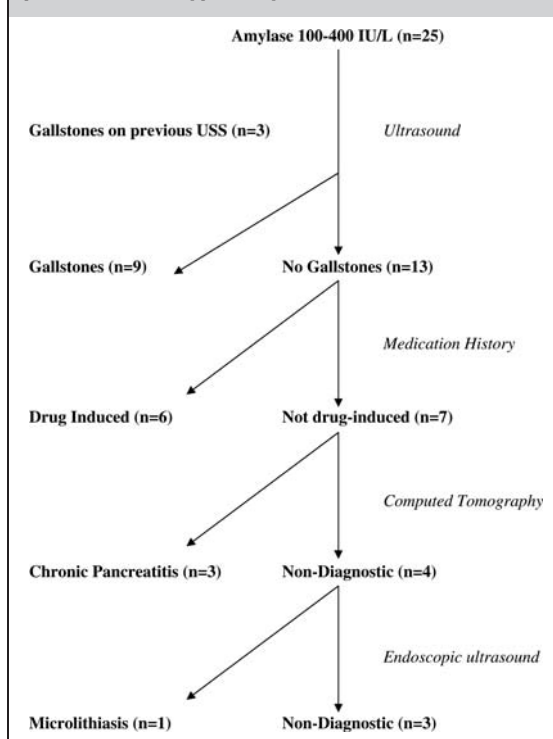
Twenty-five patients (21 men and 4 women) were identified with the combination of hyperamylasaemia (amylase 100–400 IU/L) and upper abdominal pain. The mean age of the patients was 46.7 years (range 31–71 years). The median amylase of this cohort was 230 IU/L (range 102–358 IU/L). The median time from initial pain to presentation was 2.7 days (range 0–5 days).

The investigation of these patients is summarized in Figure 1. Twenty-two patients underwent transabdominal ultrasound with gallstones identified in nine cases. The remaining three patients were known to have gallstones and were awaiting elective surgery. None of the patients without evidence of gallstones admitted to a high alcohol intake, and none had a documented family history of pancreatic disease.

Of 13 patients with no evidence of cholelithiasis, six patients were taking medications that are known to cause pancreatitis (statins [$n = 3$]; sodium valproate [$n = 1$]; azathioprine [$n = 1$]; and prednisolone [$n = 1$]).

The remaining seven patients without evidence of acute pancreatitis underwent computed tomography (CT) scans that identified chronic pancreatitis in three cases, and in four they were non-diagnostic. After disclosing the results of the CT scans to the patients with radiological evidence of chronic pancreatitis, all three admitted to significant alcohol consumption earlier in their

Figure 1
Flow diagram illustrating investigation of patients with hyperamylasaemia



adult lives. However, none reported having been admitted with acute pancreatitis on a previous occasion, and all denied admission elsewhere with pancreatitis. The four patients with normal CT scans underwent endoscopic ultrasound (EUS) to exclude microlithiasis, this being positive in one instance.

The three patients with no established cause for the hyperamylasaemia were two women aged 39 and 67 years, and a man aged 53 years. The amylase levels of the three patients were 231, 275 and 358 IU/L, respectively.

All patients with gallstones, and the patient with microlithiasis underwent cholecystectomy as definitive treatment, and none have had a recurrent admission with hyperamylasaemia. Patients believed to be suffering from drug-induced hyperamylasaemia had their medications changed to alternative agents, and have not experienced a recurrent episode of pain/hyperamylasaemia.

None of the three patients without a diagnosis have re-presented with abdominal pain during

the subsequent 5 years since their index presentation.

Discussion

The principal finding of this study is that the majority of patients 22/25 (88%) with upper abdominal pain and a hyperamylasaemia have an identifiable cause for the elevation in serum amylase. Furthermore, most of these patients 13/22 (59%) do in fact have gallstones/microlithiasis as the underlying aetiology. A significant number 6/22 (27%) had hyperamylasaemia as a result of a prescribed medication, and 3/22 (14%) had chronic pancreatitis diagnosed following investigation.

The value of serum amylase as a marker of pancreatic disease was first proposed by Elman and colleagues in 1929, and it is the most widely used diagnostic test for pancreatitis, with the majority of patients with acute pancreatitis having elevated serum amylase levels.^{5,6} Serum amylase levels become elevated within 2 to 12 hours of the onset of pain, peaking within 48 hours and then falling back to basal levels.⁷ The median time from onset of pain to presentation in the current series was 2.7 days, which may explain why some of the patients had an amylase level <400 IU/L.

In clinical practice, there is no current consensus as to the cut-off level of amylase diagnostic of acute pancreatitis. A level of at least three times the upper limit has been suggested, although levels from 2–5 times or more the upper limit have been used in recent studies.^{2,8,9} These normal values are based on the distribution of serum amylase levels within patient populations and so for a given individual, a serum amylase level <400 IU/L may still be associated with a diagnosis of acute pancreatitis. However, as the majority of patients do not go confirmatory cross-sectional imaging it is not possible to confirm this. On a practical level, the data presented in this study would suggest that patients with abdominal pain and hyperamylasaemia should certainly be investigated and treated in the same manner as patients with acute pancreatitis in accordance with the recommendations of the BSG guidelines.³

As stated above, it is clear that the value of the test to clinical practice is dependent on the

diagnostic level selected. It has been shown that the sensitivity and specificity of amylase in the diagnosis of acute pancreatitis are 91.7–100 and 91.6–97.6% when the cut-off level of amylase is set at the upper limit of normal, however if the level is set at an arbitrary 1000 IU/L then the sensitivity rises to 100%, while the specificity goes down to 60.9%.¹⁰

In only 3/25 (12%) cases in the current series was no clear aetiology identified for the hyperamylasaemia. Furthermore, if the drug-induced hyperamylasaemia cases are regarded as a mild form of pancreatitis then 88% of patients in our series had a pancreatobiliary aetiology to their elevated amylase levels. In contrast, in a study of patients with hyperamylasaemia and non-specific symptoms, 78.9% of patients had no pancreatic pathology identified and the authors concluded that the diagnostic yield was poor, questioning whether such patients warranted investigation.¹¹

The strengths of this study include an insight into a patient group that is generally underinvestigated, and a demonstration that an accurate diagnosis can be made on the majority of patients. Weaknesses may include a relatively small cohort size, and the retrospective design.

It would appear therefore that a sound history of upper abdominal pain is present especially if there is a significant interval from onset to presentation then there is likely to be an aetiology defined by following an acute pancreatitis investigative pathway.

Alternatives to serum amylase include urinary amylase and serum lipase. Amylase has a half-life of 2 hours and cleared in the urine such that the urinary amylase levels peak some 12 to 24 hours later and so may be of benefit in assessing patients presenting in a delayed manner after the peak of the serum amylase. Serum lipase levels rise earlier in the course of acute pancreatitis reaching a peak within 24 hours and a result of a longer half-life remain elevated for 8 to 14 days.⁷ As a result, like urinary amylase, it is superior to serum amylase in confirming acute pancreatitis in patients presenting late to the surgeon.¹² Furthermore, lipase has a greater sensitivity and specificity (85–100% and 84.7–99%, respectively) for pancreatitis.^{3,13} Serum lipase is in fact noted to be superior to amylase and recommended in the BSG guidelines, however, the test is not routinely available in the majority of laboratories in the UK.

Conclusions

Patients presenting on the surgical intake with epigastric pain and hyperamylasaemia not diagnostic of pancreatitis should be carefully investigated in the same way as per acute pancreatitis as gallstones will be present in at least half of the cases. If ultrasound is not diagnostic then cross-sectional imaging with CT or MRI is appropriate and in some cases EUS. Failure to investigate pancreatitis will also mean that these patients will miss out on early definitive treatment and will be at risk for further exacerbations.

It is also important, in the emergency setting, to consider other causes of hyperamylasaemia especially if the history is inconsistent with pancreatitis or gallstone disease as some conditions may warrant urgent investigation and treatment. In particular it is important to elicit an accurate drug history to identify potential aetiological agents as increasing numbers of patients are prescribed medications that may induce pancreatitis.

References

- Bradley EL 3rd. A clinically based classification system for acute pancreatitis. *Ann Chir* 1993;47:537–41
- Bollen TL, van Santvoort HC, Besselink MG, *et al.* The Atlanta classification of acute pancreatitis revisited. *Br J Surg* 2008;95:6–21
- UK guidelines for the management of acute pancreatitis. *Gut* 2005; 54 (Suppl. 3):1–9
- Whitcomb DC. Clinical practice. Acute pancreatitis. *N Engl J Med* 2006;354:2142–50
- Elman R, Arneson N, Graham EA. Value of blood amylase estimation in the diagnosis of pancreatic disease: a clinical study. *Arch Surg* 1929;19:943–67
- Pannala R, Kidd M, Modlin IM. Acute pancreatitis: a historical perspective. *Pancreas* 2009;38:355–66
- Smotkin J, Tenner S. Laboratory diagnostic tests in acute pancreatitis. *J Clin Gastroenterol* 2002;34:459–62
- Acosta JM, Katkhouda N, Debian KA, Groshen SG, Tsao-Wei DD, Berne TV. Early ductal decompression versus conservative management for gallstone pancreatitis with ampullary obstruction: a prospective randomized clinical trial. *Ann Surg* 2006;243:33–40
- Mery CM, Rubio V, Duarte-Rojo A, *et al.* Android fat distribution as predictor of severity in acute pancreatitis. *Pancreatol* 2002;2:543–9
- Kiriyama S, Gabata T, Takada T, *et al.* New diagnostic criteria of acute pancreatitis. *J Hepatobiliary Pancreat Sci* 2010;17:24–36
- Byrne MF, Mitchell RM, Stiffler H, *et al.* Extensive investigation of patients with mild elevations of serum amylase and/or lipase is 'low yield'. *Can J Gastroenterol* 2002;16:849–54
- Orebaugh SL. Normal amylase levels in the presentation of acute pancreatitis. *Am J Emerg Med* 1994;12:21–4
- Nordestgaard AG, Wilson SE, Williams RA. Correlation of serum amylase levels with pancreatic pathology and pancreatitis etiology. *Pancreas* 1988;3:159–61

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