ABNORMAL LABORATORY RESULTS

Blood tests for acute pancreatitis

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SUMMARY

The diagnosis of acute pancreatitis requires the presence of at least two of the three diagnostic criteria – characteristic abdominal pain, elevated serum amylase or lipase, and radiological evidence of pancreatitis.

Serum concentrations of amylase and lipase rise within hours of the pancreatic injury. A threshold concentration 2–4 times the upper limit of normal is recommended for diagnosis.

Serum lipase is now the preferred test due to its improved sensitivity, particularly in alcohol-induced pancreatitis. Its prolonged elevation creates a wider diagnostic window than amylase.

Neither enzyme is useful in monitoring or predicting the severity of an episode of pancreatitis in adults.

New biomarkers including trypsinogen and elastase have no significant advantage over amylase or lipase.

Introduction

Acute pancreatitis can be a diagnostic challenge given the non-specific nature of the symptoms and widely varying results of investigations. The diagnosis typically involves a combination of history and examination, abnormal laboratory investigations and radiological evidence of pancreatic inflammation.

An elevation in the serum amylase or lipase is a key element in the diagnosis, but needs to be interpreted with caution. There may be other potential causes for these enzymes to be elevated. The sensitivity of the test is also affected by the timing of the testing and the underlying cause of the pancreatitis. Although serum amylase was the primary diagnostic marker, serum lipase is now the preferred test.

Pathophysiology

Pancreatitis is thought to occur as a consequence of premature, intra-pancreatic activation of pancreatic proenzymes. These include chymotrypsinogen, procolipase, prophospholipase A2 and proelastase. The proenzymes are synthesised by the acinar cells and stored in vesicles known as zymogens. They are released into the pancreatic duct and activated at the brush border of the duodenal enterocytes.

The specific mechanisms by which the various aetiologies of pancreatitis cause this premature activation of proenzymes are not well understood. It appears that 'autodigestion' starts a local inflammatory response. The release of proinflammatory and chemotactic mediators, the activation of macrophages and the influx of other inflammatory cells damage the pancreas. Systemic complications such as bacteraemia, acute respiratory distress syndrome and a systemic inflammatory response syndrome may also occur if the various mediators enter the systemic circulation.[1,2]

Diagnostic criteria

The diagnosis of acute pancreatitis usually requires a combination of clinical, laboratory and radiological findings. A number of international guidelines have suggested two of the following three features are required for the diagnosis:[3,4]

- abdominal pain consistent with acute pancreatitis (acute onset of persistent severe epigastric pain often radiating to the back)
- serum lipase activity (or amylase activity) at least three times greater than the upper limit of normal
- characteristic findings of acute pancreatitis on abdominal ultrasound (a CT scan or MRI is considered if the diagnosis is uncertain).

Serum amylase

Serum amylase is secreted in specific isoforms by the salivary glands (s-amylase) and pancreas (p-isoamylase). It predominantly acts to digest starch, glycogen and related polysaccharides. Almost all laboratories currently measure total serum amylase so the result includes both isoenzymes. The reference range is typically 20–300 U/L, but does vary with age and gender. It also varies between laboratories despite attempts to adopt standardised reference methods.

In studies using radiological evidence as the 'gold standard' for acute pancreatitis, serum amylase has a sensitivity of 81–95%. However, this does depend

on the definition of 'abnormal' and the cut-off values chosen. Most guidelines now suggest an amylase concentration 2–4 times the upper limit of normal is optimal for diagnostic accuracy, but this may reduce the sensitivity of the test to as low as 60%.[2,3,5] The sensitivity is also influenced by other factors, including the timing of the test and the cause of the pancreatitis.

Timing

In acute pancreatitis, amylase can rise rapidly within 3–6 hours of the onset of symptoms, and may remain elevated for up to five days. However, it has a short half-life of 12 hours so the concentration can normalise within 24 hours. This significantly reduces its value as a diagnostic test relatively early in the clinical course.

Cause of pancreatitis

In pancreatitis due to hypertriglyceridaemia, the serum amylase can be normal in up to 50% of cases. This is due to interference with the assay by either a circulating inhibitor or the hyperlipidaemia itself. A number of studies have also suggested that amylase may be less elevated in alcohol-induced pancreatitis compared to other causes.

Many conditions (see Table) can increase serum amylase so it is not specific for pancreatitis. These conditions include various intra- and extra-abdominal illnesses and drugs. Macroamylasaemia is an uncommon condition in which amylase rises because its clearance is reduced.[1,2,5]

Given that up to 60% of the total serum amylase originates from non-pancreatic sources, measuring the pancreatic isoenzyme may improve the diagnostic accuracy in acute pancreatitis. However, this isoenzyme also rises in many of the other non-pancreatic causes of hyperamylasaemia. There are few studies on whether measuring the isoenzyme significantly improves the diagnostic accuracy of acute pancreatitis.[2,5] Consequently, pancreatic amylase is not routinely measured in most laboratories.

Serum lipase

Lipase has now replaced amylase as the biochemical test of choice in acute pancreatitis.[4] With an important role in fat digestion, the tissue concentration of lipase in the pancreas is 100-fold higher than in other tissues such as the duodenum, stomach, adipose tissue and lung.

Serum lipase typically increases 3–6 hours after the onset of acute pancreatitis and usually peaks at 24 hours. Unlike amylase, there is significant reabsorption of lipase in the renal tubules so the serum concentrations remain elevated for 8–14 days. This means it is far more useful than amylase when the clinical presentation or testing has been delayed by more than 24 hours. Serum lipase also has a greater sensitivity than amylase in patients with alcoholic pancreatitis. A number of studies suggest its sensitivity is 85–100%.

There are a number of other conditions that can elevate lipase including pancreatic disease, cholecystitis, intestinal ischaemia, renal impairment and malignancy (Table). However, the test's specificity has been shown to be higher than amylase testing in several studies.[1-3,5] Depending on the cut-offs, specificity may be higher than 95%.

Like serum amylase, there is some variability in the reference ranges for lipase, and debate about the

Table **Causes of elevated serum amylase and lipase** [2,5]

Causes	Amylase	Lipase
Abdominal conditions	acute pancreatitis, pancreatic trauma, perforated viscus, intestinal infarction and obstruction, peritonitis, acute cholecystitis, appendicitis, hepatitis, abdominal aortic aneurysm, ruptured ectopic pregnancy, fallopian and ovarian cysts	acute pancreatitis, pancreatic trauma, perforated viscus, intestinal infarction and obstruction, peritonitis, acute cholecystitis, appendicitis, hepatitis, abdominal aortic aneurysm, malignancy (especially oesophagus, stomach, duodenum, pancreas)
Extra-abdominal conditions	salivary disease, renal failure, ketoacidosis, pneumonia, cerebral trauma, burns, anorexia nervosa and bulimia	renal failure, ketoacidosis, fat embolism, bony fractures
Drug induced	azathioprine*, colaspase, sulphonamides, tetracycline*, didanosine, methyldopa*, oestrogens*, frusemide, 5-aminosalicyclic acid*, valproate*, thiazides*, glucocorticoids, nitrofurantoin*, rifampicin*, tacrolimus*, metronidazole*, 6-mercaptopurine*, cyclosporin*, cisplatin*	adrenocorticotropic hormone*, tetracycline*, oestrogens, frusemide*, valproate*, thiazides*, rifampicin*, metronidazole*, zalcitabine, opioids, methylprednisolone*, indomethacin*
Others	macroamylasaemia, idiopathic hyperamylasaemia	mumps, hyperlipoproteinaemia

* These drugs can cause acute pancreatitis, but can also elevate pancreatic enzymes without pancreatitis.

optimal cut-off value that should be used to diagnose acute pancreatitis. Most guidelines now recommend 2–3 times the upper limit of normal as the most appropriate cut-off.[2,3]

Combined testing

In clinical practice it is not uncommon to see a combination of amylase and lipase being measured. Most guidelines do not advocate this approach as the increase in sensitivity achieved over a single test is only marginal and not cost-effective.

The ratio of the two enzymes may sometimes be useful in establishing the cause of the pancreatitis. Some studies suggest that a lipase–amylase ratio of more than 2–3:1 is more indicative of alcoholic pancreatitis, while a ratio of less than 1:2 is more likely to be related to gallstones.[2,5] In an acute exacerbation of chronic pancreatitis neither enzyme may be elevated.

The magnitude of the elevation of amylase and lipase does not predict disease severity in adults. Ongoing daily measurements should not be used as a guide of disease activity or resolution. A serum C-reactive protein (CRP) greater than 150 mg/L measured 48 hours after the onset of symptoms is the best single laboratory predictor of disease severity,[6] while a number of scoring systems that are a composite of clinical and laboratory criteria (Ranson's,[7] BISAP,[8] APACHE,[9] Glasgow[10]) have also been devised for this purpose.

In children, lipase may be related to severity. One Australian paediatric study found that a lipase more than seven times the upper limit of normal in the first 24 hours could predict severe acute pancreatitis.[11]

Other markers

A number of other pancreatic enzymes and inflammatory biomarkers have been evaluated for their diagnostic value in acute pancreatitis. These include trypsinogens, phospholipase A2, pancreatic elastase, urine trypsinogen activated protein and carboxypeptidase B.

Trypsinogen is the best studied, with concentrations rising in the serum and urine within a few hours of the onset of pancreatitis. The sensitivity is estimated to be over 90% and the specificity is over 83%. However, this test along with most of the other new biomarkers appears to offer little advantage over lipase and amylase in terms of diagnostic accuracy.[2,5]

Conclusion

Serum concentrations of amylase and lipase rise within hours of an episode of acute pancreatitis. They are key components of the diagnostic criteria along with abdominal pain and radiological findings.

Lipase is now preferred over amylase due to a higher sensitivity, particularly in cases of pancreatitis due to alcohol and hypertriglyceridaemia. It also tends to remain elevated for longer than amylase, making it more useful when the presentation has been delayed by more than 24 hours.

Both enzymes may be elevated in various conditions other than pancreatitis. Neither is useful in monitoring the disease course or predicting severity in adults.

Conflict of interest: none declared

Q:

SELF-TEST QUESTIONS

True or false?

5. The severity of acute pancreatitis in adults can be monitored by serial measurements of serum lipase.

6. A rise in the pancreatic amylase isoenzyme can be caused by conditions other than acute pancreatitis.

Answers on page 143

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