Familial hyperamylasaemia

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Abstract

A six year old boy underwent extensive investigation for recurrent abdominal pain and was found to have a persistently raised serum amylase. Endoscopic retrograde cholangiopancreatography was normal and macroamylasaemia was excluded. Serum amylase concentrations were found to be raised in other family members spanning three generations, all of whom were asymptomatic. Clearance studies suggested no evidence of a renal tubular defect and serum lipase concentrations were normal. This is the first report of apparently familial hyperamylasaemia and the mode of inheritance is consistent with an autosomal dominant pattern.

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Although a greatly raised serum amylase in a patient with abdominal pain is most often due to pancreatic disease, there are many recognised causes of a mildly raised concentration.¹ We report a hitherto undescribed cause of hyperamylasaemia.

Methods

INDEX CASE

In 1993, a four year old white boy presented acutely with colicky periumbilical pain, lethargy, anorexia, and vomiting. He had experienced several similar episodes during the

previous year, each resolving after a few hours with simple analgesics. Between episodes he was well. As an infant he had been investigated for poor weight gain, vomiting with occasional loose stools, and a persistent cough. Routine haematology and biochemistry, liver and renal function tests, serum ferritin and vitamin B12, thyroid function tests, urine and stool microbiology, a sweat test, xylose absorption test, chest radiography, and barium meal had been normal. At two years his persistent symptoms prompted an upper gastrointestinal endoscopy and jejunal biopsy, which were normal. Subsequently, his problems resolved and his growth became normal with height and weight increasing between the 10th and 25th centiles.

On admission, he had a mild pyrexia with no signs of an acute abdomen. Routine investigations were normal except for a slightly raised serum amylase of 168 Somogyi U/dl (normal range 40–160 U/dl). A plain abdominal radiograph and ultrasound scan were normal. A laparoscopy disclosed no pathology and a non-inflamed appendix was removed. Six weeks later he was readmitted with recurrent abdominal pain and a repeat serum amylase was raised at 336 Somogyi U/dl but a repeat abdominal ultrasound scan again showed no abnormality. His pain settled and outpatient investigations including a small bowel meal, abdominal computed tomography, sweat test, and DNA analysis for common cystic fibrosis gene mutations were all normal. His serum amylase remained raised at 226 Somogyi U/dl and he was referred to us for further investigation.

During the next year he remained well but his serum amylase was raised at 160 international units/l (normal range 19–95 IU/l). He had a normal lipid profile, liver function tests, urine metabolic screen, faecal chymotrypsin, and faecal fat content. Endoscopic retrograde cholangiopancreatography showed normal ductal anatomy with a normal pancreaticobiliary junction. Macroamylasaemia was considered likely after finding a normal urinary amylase excretion (38 IU/4 h) in the presence of a persistently raised serum amylase (149 IU/l).² Macroamylasaemia was definitively excluded by the absence of diffuse streaking in the γ -globulin region after electrophoretic separation on cellulose acetate.³ Autoantibodies, rheumatoid factor, and Ro and La antigens were negative. Currently the child is well with normal growth. He has had no further attacks of non-specific abdominal pain. During a three year period, the patient's serum amylase was estimated on multiple occasions by various standard laboratory methods⁴ and was found to be consistently raised (Fig 1).

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Figure 1: Serial serum amylase concentrations for the index case. *Serum amylase is expressed as the ratio of the measured value to the upper limit of the normal range.

Figure 2: Family pedigree with serum amylase results. Reference range for white subjects 19–95 IU/l. *Increased concentration recorded on several occasions.

FAMILY MEMBERS

Blood was taken from his grandfather, father, mother, sister, and brother, who were all well and taking no regular medication. They were all white. The patient's father had a normal serum amylase of 68 IU/l and his two year old brother's serum amylase was at the top of the normal range at 95 IU/l (normal range 19–95 IU/l). His mother, half sister, and maternal grandfather had significantly raised concentrations at 144 IU/l, 138 IU/l, and 112 IU/l respectively (Fig 2). Further blood samples from our index case and his mother were analysed at a national amylase reference laboratory. Hyperamylasaemia was confirmed in both subjects, with raised salivary and pancreatic isoforms^{4 5} (Table). Clearance studies indicated no evidence of a renal tubular defect in either subject and serum lipase concentrations were normal. Finally, as both the amylase protein and ABO blood group proteins are encoded on chromosome 1, blood grouping was checked. It was only possible to obtain the ABO blood group of the index case, his mother, and half sister, but they were found to be dissimilar (group O, rhesus positive in index case and group A, rhesus positive in the others).

Discussion

This is the first description of apparently familial hyperamylasaemia, with evidence of the condition in at least four family members spanning three generations. The pattern of inheritance indicates an autosomal dominant condition and, given the younger brother's age

and amylase concentration, he too is likely to have inherited the condition. Despite the lack of uniformity in measurement of serum amylase in laboratories throughout the United Kingdom,⁶ the serum amylase concentrations in our subjects were consistently raised over several years and also when measured by different techniques in different laboratories. The origin of the hyperamylasaemia is uncertain but must result either from an increased rate of entry of amylase into the circulation, or a decreased metabolic clearance of the enzyme, or both. Genetic factors are known to be important as there exist racial variations in the normal range of serum amylase.⁷ The pancreas and salivary glands account for almost all of the serum amylase activity in normal persons and both pancreatic and salivary isoforms were raised in the index case and his mother. Renal clearance results did not suggest a renal tubular defect in amylase excretion and macroamylasaemia, a recognised pitfall in this situation, was excluded.^{8–10} There is no evidence that macroamylasaemia is an inherited condition.²

Familial hyperamylasaemia must now be added to the long list of conditions other than pancreatic disease which can cause a raised serum amylase⁴ and for which there was no evidence in any of the family members. Knowledge of these conditions is important so that appropriate investigations are undertaken in patients with a raised serum amylase. Although there may be hazards from over-investigating patients with a raised serum amylase, and familial hyperamylasaemia is likely to be rare, the consequences of overlooking a raised serum amylase concentration in a child are potentially serious.¹¹

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Amylase isoforms and clearance studies in index case and mother

	Total amylase (U/l)	Pancreatic amylase* (U/l)	Salivary amylase (U/l)	Amylase/creatinine clearance ratios (%)**	Serum lipase (U/l)
Index case	273 (70–200)	96 (<65)	177 (<125)	1.1 (1.0–3.0)	30 (5–65)
Mother	314 (70–200)	138 (50–120)	176 (<125)	1.9 (1.0–3.0)	37 (5–65)

Normal range in parentheses.
*Reference range from Fisbach and Zawla.⁵
**Urinary amylase / Serum amylase $\times$ Serum creatinine / Urinary creatinine $\times$ 100