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Reminder of important clinical lesson

A very high amylase can be benign in paediatric Crohn's disease

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Summary

A 12.5-year-old boy with Crohn's disease with abdominal pain had a raised amylase of 1835 IU/l with normal lipase levels. Ultrasound showed no evidence of inflammation of pancreas. The amylase to creatinine clearance ratio, was 0.8% (reference interval 2%–5%; >6% consistent with acute pancreatitis; <1.6% with macroamylasemia), suggesting he had raised serum amylase with a corresponding reduced clearance of amylase in his urine, positively supporting the diagnosis of macroamylasemia. Macroamylasemia has no clinical significance other than misdiagnosis as acute pancreatitis. Awareness of this condition is important and a positive diagnosis should always be made to avoid unnecessary changes in treatments.

BACKGROUND

Pancreatitis is a rare disease in children which carries significant morbidity and mortality. The overall incidence of pancreatitis is on the rise[1–4] and the risk of developing pancreatitis is increased in inflammatory bowel disease (IBD). Potential factors for developing pancreatitis in IBD include duodenal inflammation, extra-intestinal causes and drug treatments like aminosalicylates, corticosteroids, azathioprine and 6-mercaptopurine.[5–8] In a 10 year report of 279 children with pancreatitis, five had IBD[5] whereas only two IBD cases were identified in a paediatric pancreatitis cohort of 271 children from another centre.[3]

Plasma amylase is a sensitive marker for acute pancreatitis,[9] and regular monitoring is important in children with inflammatory bowel disease. Plasma lipase is a useful back-up test if there is a strong clinical suspicion of pancreatitis when amylase levels are equivocal.[9] This is because lipase rises more slowly and persists for a week after the onset of symptoms. Pancreatic imaging, such as ultrasound, provides further reassurance, and abnormalities would suggest an alternative diagnosis to benign hyperamylasaemia.[9] In the reported case, a child with Crohn's disease had significantly raised plasma amylase, without typical symptoms of acute pancreatitis.

CASE PRESENTATION

A 12.5-year-old boy, diagnosed with ileo-colonic Crohn's disease on ileocolonoscopy and histology 5 months earlier, was reviewed in a routine follow-up in the Paediatric Gastroenterology clinic. His active disease had been successfully treated with exclusive enteral nutrition for 8 weeks with return to normal diet. At this appointment he reported episodes of abdominal pains which lasted a few minutes, but either resolved spontaneously or following defaecation. His bowel habits were normal, and he was otherwise well and active. He was on regular 5-ASA derivatives (Pentasa) and polymeric enteral feed supplements. He had not had any steroid treatment, and was not on concomitant immunosuppressants. He had continued to thrive with the only finding on examination being some non-specific guarding but no overt tenderness in the peri-umbilical area. There was no evidence of oral or perianal ulceration or other extra-intestinal systemic involvement. The salivary glands were not swollen or tender. His blood results (albumin 37, C reactive protein 8, erythrocyte sedimentation rate 15 and white cell count 12.3 with N7.5, platelets 412×10^9/l, alanine transaminase 14 IU/l, γ glutamyl transpeptidase 10 IU/l) were within the normal range. His Crohn's disease was in remission with a Paediatric Crohn's Disease Activity Index[10] score of 5.

Blood results available later in the day however, showed a raised amylase of 1835 IU/l (reference range 36–128). He was therefore recalled for a reassessment, with a presumptive diagnosis of acute pancreatitis. There was no change from the clinical findings earlier in the day and he remained well. Amylase on a repeat blood sample was again high (1893 IU/l), however plasma lipase was normal (23 IU/l; reference range 5–65 IU/l). Plasma creatinine was 54 umol/l; reference range 80–115 umol/l). On ultrasound of the pancreas there was no evidence of swelling of pancreas or bowel thickening. In the absence of any evidence to support a diagnosis of acute pancreatitis, or non-pancreatic cause of hyperamylasemia, it was suspected that the high plasma amylase was due to macroamylasemia. The amylase to creatinine clearance ratio (ACCR), determined from amylase and creatinine concentrations on paired blood and random urine samples was 0.8% (reference interval 2%–5%; >6% consistent with acute pancreatitis; <1.6% with macroamylasemia). Plasma amylase had fallen to 114 IU/l (reference 36–128 IU/l) 3 weeks later.

DIFFERENTIAL DIAGNOSIS

1. Pancreatitis (related to drug intake eg, aminosalicylates, thiopurines for inflammatory bowel disease)
2. Macroamylasaemia: macrocomplex molecule formation with amylase leading to impaired excretion via kidneys
3. Familial hyperamylasaemia: ruled out as repeat bloods in 3 weeks showed normalisation of amylase levels

4. Raised amylase due to exogenous causes such as salivary gland inflammation in mumps.

TREATMENT

Conservative monitoring of amylase levels, no active treatment.

OUTCOME AND FOLLOW-UP

He was discharged without changes in medications. Three weeks later the abdominal symptoms had settled and plasma amylase had fallen to 114 IU/l (normal). Serum IgA was marginally raised at 3.4 g/l (reference 0.8–2.8 g/l) very similar to the value of 4.0 g/l when Crohn's disease was diagnosed. Serum IgG and IgM were normal on both occasions. Subsequent plasma amylase levels have been persistently normal.

DISCUSSION

Macroamylasemia is a biochemical abnormality which results from aggregation of circulating amylase with immunoglobulins, usually IgA (92%) but sometimes IgG.[11–13] The binding site is usually to Fab portion of immunoglobulin. Macrocomplexes with IgM, IgE or IgE have not been identified though other molecules including α 1 antitrypsin, polysaccharides and glycoproteins have been implicated.[14] Normally, amylase with molecular mass of approximately 55000 Daltons, is readily filtered by the renal glomeruli. However, aggregation increases the mass to 150 000–1 000 000 Daltons and macromolecules are not filtered. Plasma amylase increases and urinary amylase is lower than normal.[15] In the absence of renal failure, a low amylase/creatinine clearance ratio is diagnostic.[11] In contrast, in acute pancreatitis, renal tubular reabsorption of amylase and other proteins is reduced and the albumin/creatinine clearance ratio is increased above normal.[16] Thus, estimation of the ratio is a simple test, to help differentiate between pancreatitis and macroamylasemia.

Macroamylasemia has no clinical significance other than misdiagnosis as acute pancreatitis. Many cases have been detected during investigation of abdominal pain, but this does not establish a causal relationship.[17] It has been hypothesised that the abdominal pains associated with macroamylasemia may be due to the precipitation of the large macroamylase molecules within the pancreas[18] but this remains largely unproven. In adults, macroamylasemia was reported in 2.5 per cent of all hyperamylasemic patients, and 1 per cent of apparently healthy subjects with normal amylase levels.[19] It has been associated with celiac disease, lymphoma, HIV infection, monoclonal gammopathy, rheumatoid arthritis and ulcerative colitis. In children, there are reports of cases with celiac disease,[20] and lymphoma in Wiskott Aldrich syndrome.[21]

This is the first known report in a child with Crohn's disease. In this case, amylase may have complexed with IgA, which was marginally raised. Macroamylasemia resolved within 3 weeks' without any treatment. In the absence of typical clinical symptoms of pancreatitis or salivary gland inflammation, and with normal plasma lipase, non-pancreatic causes of hyperamylasemia should be considered. Imaging investigations including ultrasound, CT scan and monitoring of amylase levels and checking renal excretion of amylase might aid diagnosis. Macroamylasemia must be recognised to avoid a misdiagnosis of pancreatitis. This is particularly important in children with inflammatory bowel disease to avoid an unnecessary change in their treatments which could lead to a potential relapse.

Learning points

- Macroamylasemia is a benign condition where raised amylase levels are not related to pancreatic injury. It is a biochemical abnormality, resulting from aggregation of circulating amylase with immunoglobulins (mainly IgA), leading to reduced urinary excretion of amylase, with a low amylase to creatinine clearance (<1.6%).
- Macroamylasemia has no clinical significance other than misdiagnosis as acute pancreatitis.
- Awareness of this condition is important and a positive diagnosis should always be made to avoid unnecessary changes in treatments.

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Competing interests None.

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