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DIAGNOSING MACROAMYLASEMIA IN UNEXPLAINED HYPERAMYLASEMIA

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Macroamylasemia is a curious condition marked by hyperamylasemia without any other signs or symptoms, most frequently caused by immunoglobulin-amylase complexes that cannot be secreted normally by the kidneys. It usually requires no additional investigation, but must be taken into consideration to avoid unnecessary diagnostics and treatment, which burden both the patient and the healthcare system. A number of studies and reports have described macroamylasemia in combination with other conditions or diseases, one of the more interesting being celiac disease, where a gluten free diet was shown to cure both. Our case presents a young female patient without significant signs or symptoms except for elevated serum amylase discovered by chance, and ignored. Macroamylasemia was considered and confirmed, while celiac disease was subsequently excluded.

Key words: hyperamylasemia, laboratory diagnosis, macroamylasemia

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INTRODUCTION

Macroamylasemia, a rare but otherwise benign condition, is characterized by hyperamylasemia or elevated serum amylase levels without elevated urine amylase and other signs or symptoms (1-6). In macroamylasemia, amylase is bound by immunoglobulin, making it larger than usual and unable to be filtered by the kidneys, resulting in high serum amylase levels but normal urine levels (1-6). Various papers report different statistics on the incidence of macroamylasemia, it is clear that it is more common among adults, although cases in infants and children have been reported. As hyperamylasemia is the cornerstone for diagnosing pancreatitis, a much more serious condition that requires additional work-up and in most cases hospitalization, it is important for physicians at the primary or secondary level to be able to recognize and diagnose macroamylasemia in order to avoid further diagnostic and treatment measures, or to avoid changing current treatment when considering comorbidity (1-4,7). Further testing puts unnecessary strain on various areas of the healthcare system taking time for work with other patients, not to mention the stress on patients, especially when further investigation or treatment is generally not required (1-4,7).

An accepted algorithm for confirming a diagnosis of macroamylasemia, after first finding elevated serum amylase without elevated urine amylase, is to subsequently test for serum lipase, which together with high amylase levels usually suggests pancreatitis (1-4,6,8). If serum lipase is normal, kidney function must be tested, as abnormal renal function would also cause elevated levels (1-4,6). Once normal kidney function is confirmed, renal amylase clearance relative to cre-

atinine clearance should be calculated (see Appendix); normal ratios are between 3% and 5%, where a result of less than 1% suggests macroamylasemia (1-4,6,8). The final confirming test is electrophoresis or polyethylene glycol precipitation test and chromatography (1,2,8,10). Unfortunately, these methods are not routinely used, at least not in Croatia, and laboratories are not offering or performing such tests, but most authors would agree that the ratio calculation can be considered diagnostic, although there is disagreement about the issue (2,4-9,11).

CASE REPORT

A 27-year-old female patient visited doctor's office for the first time. The patient had no complaints other than known fatigue due to sideropenic anemia from menstrual bleeding, which the patient regularly followed-up with laboratory tests (blood count, iron, UIBC, TIBC and ferritin levels), and was taking iron as needed. The patient described gastroesophageal reflux disease (occasional nausea, heartburn and abdominal pain), and was aware of elevated serum amylase without elevated urine amylase after routine check-up with laboratory tests a couple of years before. No further investigation was undertaken, but the patient regularly underwent laboratory testing for serum and urine amylase, and the results were always the same. Her appetite, urine and stool were normal. Menstrual cycles were normal, some cycles were abundant, but her last gynecologic examination was normal. The patient did not smoke or drink. Allergies were denied and the patient did not take any regular medication. The patient denied other serious conditions or diseases except for scoliosis that was followed-up, treated with an orthosis and physical therapy, and operated due to severity. She also denied any other significant medical history except for multiple hospitalizations (more than five) as a child due to abdominal pain, nausea and vomiting that had led to severe dehydration, but no further explanation or diagnosis had ever been found. Family history was unremarkable.

Examination of her previous medical documentation confirmed the patient's interview, including multiple hospitalizations for vomiting and severe dehydration. Several tests were performed during this time (laboratory tests, upper gastrointestinal series, abdominal ultrasound) and all proved normal, with the exception of hiatal hernia, and metabolic acidosis and acetonuria. Test results for serum and urine amylase were also found and both were within the reference values: serum amylase 90 U/L (ref. <90) and urine amylase 339 U/L (ref. <390).

Physical examination was unremarkable. Fresh laboratory test results, just as the patient described, showed elevated serum amylase 143 U/L (ref. 23-91) but normal urine amylase 57 U/L (ref. <400). Follow up laboratory test for serum lipase was normal, 44 U/L (ref. 13-60). Renal function was normal and renal amylase clearance relative to creatinine clearance was calculated (see Appendix) and found to be 0.8% (ref. 3%-5%). Although the aforementioned hospitalizations were initially misleading, the interview, physical examination and test results suggested the diagnosis of macroamylasemia to be very likely; only electrophoresis was lacking.

Laboratory tests for celiac disease were negative: serum IgA 1.3 g/L (ref. 0.7-4.0) and anti-tissue transglutaminase-IgA (anti-tTG-IgA) <2 RU/mL (ref. negative <20, positive >20).

DISCUSSION

Amylase is an enzyme that is responsible for the breakdown of amylase and other starches during digestion. It exists as three subtypes, where α-amylase is found in animals, including humans, and it is the only one of clinical importance (6).

Although hyperamylasemia is associated with pancreatitis in particular, there are other conditions and diseases that may present with hyperamylasemia as well, all of which would require further investigations, unlike macroamylasemia, including sialadenitis, pulmonary disease, ovarian cysts, ruptured ectopic pregnancy, abdominal trauma, mesenteric infarction, perforated peptic ulcer, appendicitis, pelvic inflammatory disease, renal failure, mumps and carcinoma (1,2,6,8,12). Things can get tricky when macroamylasemia is found in cases that would normally present with hyperamylasemia, as in a case of appendicitis presenting with hyperamylasemia as caused by macroamylasemia (6). Another interesting case found macroamylasemia in a patient with elevated serum amylase levels, elevated urine levels and a raised clearance ratio, not characteristic of macroamylasemia. After various tests, it was concluded that elevated serum amylase levels were due to macroamylasemia, while urine values were due to salivary amylase being produced by renal cell carcinoma (12). Naturally, these patients exhibited other signs and symptoms which suggested comorbidity (6,12). Some studies report an increased incidence of macroamylasemia in HIV positive patients, but at least one study refutes this fact (13). Macroamylasemia has been reported in a case of splenosis after post-traumatic splenectomy (14). Macroamylasemia was even found while following a case of pancreatitis itself (15).

Although macroamylasemia is generally asymptomatic, a number of cases were detected due to abdominal pain, which led to serum and urine amylase measurement, but this does not confirm a relationship between the two (2,6,10). Some authors suggest it is merely a coincidence, since amylase is tested more often when abdominal pain is present (2,10). According to one hypothesis, abdominal pain and macroamylasemia are often found together due to precipitation of macroamylase molecules within the pancreas, although it has not yet been proven (2,6).

Finding hyperamylasemia with other autoimmune conditions or diseases is not uncommon either, and could indicate macroamylasemia instead of pancreatitis or hyperamylasemia associated conditions; examples are systemic lupus erythematosus, rheumatoid arthritis, and ulcerative colitis (2,5,7,16). There also is a case reported in combination with Crohn's disease (7). Many cases of macroamylasemia have been reported together with celiac disease, and one case has even been reported with both celiac disease and myasthenia gravis (5,17-19). A gluten free diet, gluten being the trigger causing celiac disease, has been shown to treat macroamylasemia in these cases (17-19). There are cases of macroamylasemia reported in selective IgA deficiency (20).

There are theories on how macroamylase is formed; one is the antigen driven theory where a self antigen cross reacts with an antibody for a foreign antigen, and the other theory is dysregulation of immune tolerance that occurs in autoimmune diseases (2,5,16,20). In this way, antibodies are formed, in most cases immunoglobulin A, rarely immunoglobulin G, which react to either salivary or pancreatic amylase, or a combination of the two, forming immune complexes, more commonly salivary amylase (2,4,7,9,15). Cases of macroamylasemia and macrolipasemia have also been described, which especially create confusion as elevated amylase and lipase are found in pancreatitis (15,21). Other molecules including α-1 antitrypsin, polysaccharides and glycoproteins have been shown to form complexes with amylase causing macroamylasemia as well (2,7,9,22).

It has also been suggested that polyclonal gammopathy or polyclonal increase of immunoglobulins, often present in autoimmune and lymphoproliferative diseases, may also increase the likelihood of developing macroamylasemia (2,15). Indeed, the condition has been associated with lymphoma, multiple myeloma and myeloid leukemia (5,7,14,15). Although most authors agree that macroamylasemia is a benign condition, diagnosed easily enough, which does not require further investigation or treatment, due to the correlation between polyclonal gammopathy and macroamylasemia it has been suggested that macroamylasemia without any clear cause deserves investigation to rule out autoimmune or lymphoproliferative disease (2,15).

Macroamylasemia may also be induced, as shown by one study where a group of test subjects were infused with a hydroxyethyl starch (HES) solution, which is a volemic colloid used in the management of hypovolemia. The test subjects were all healthy individuals who developed hyperamylasemia after infusion with a HES solution. Hyperamylasemia was proven to be of a macroamylase character. As the HES molecules broke down, hyperamylasemia or macroamylasemia resolved itself. This study proved macroamylasemia to have a potential to be induced iatrogenically as well, apart from disease (2,22).

Some papers report that actually there are three types of macroamylasemia, i.e. classic type (type 1), where serum amylase is elevated, and urine is normal; type 2, where both are elevated; and type 3, where both are normal, but these types have not been studied additionally (2,11).

In cases of serum amylase activity over 100 U/L, macroamylasemia can be confirmed by electrophoresis (1,3). A negative result shows two clearly defined bands (S and P type amylase), while the presence of a 'smeared' band, caused by an immunoglobulin-amylase complex, confirms macroamylasemia (8,10,21,23).

It should be noted that other cases of asymptomatic hyperamylasemia have been described including chronic non-pathological hyperamylasemia of pancreatic origin, ethnic hyperamylasemia, and familial hyperamylasemia (24).

Macroamylasemia fitted our case perfectly, as there were no other symptoms or signs other than elevated serum amylase to suggest pancreatitis or one of the other aforementioned conditions or diseases. Additional simple and inexpensive laboratory tests and calculations (lipase, renal function, renal amylase clearance relative to creatinine clearance) confirmed the diagnosis despite the lack of a confirming test such as electrophoresis, as all evidence clearly pointed to macroamylasemia. However, upon seeing elevated serum amylase, a physician who does not take macroamylasemia into consideration would be forced to investigate, ordering unnecessary tests and examinations. It is unclear why hyperamylasemia was originally ignored in our case, but definitive benign diagnosis was certainly welcome. Celiac disease was considered due to the connection found in the aforementioned cases and studies between macroamylasemia and celiac disease, and the presentation of atypical features of celiac disease in our patient (nonspecific gastrointestinal complaints, iron deficiency anemia and short stature), but was excluded with additional laboratory tests for serum IgA and anti-tTG-IgA.

APPENDIX

Renal amylase clearance relative to creatinine clearance:
Serum creatinine 60 μmol/L (ref. 49-90)
Urine creatinine 2.9 mmol/L (no reference for random sample)
Serum amylase 143 U/L (ref. 23-91)
Urine amylase 57 U/L (fef. <400)

Formula = urine amylase / serum amylase x serum creatinine / urine creatinine x 100
= 57 U/L / 143 U/L x 60 μmol/L / 2900 μmol/L x 100
= 0.40 x 0.02 x 100
= 0.80%

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S A Ž E T A K

DIJAGNOSTICIRANJE MAKROAMILAZEMIJE KOD NERAZJAŠNJENE HIPERAMILAZEMIJE

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Makroamilazemija je zanimljivo stanje obilježeno hiperamilazemijom bez ikakvih drugih znakova ili simptoma, najčešće uzrokovana kompleksima imunoglobulina i amilaze koji se ne mogu izlučiti putem bubrega. Najčešće ne zahtijeva proširenu kliničku obradu, ali se mora uzeti u obzir kako bi se izbjegla nepotrebna dijagnostika i liječenje koji mogu predstavljati opterećenje za bolesnika i zdravstveni sustav. Nekoliko studija i prikaza opisuju makroamilazemiju zajedno s drugim stanjima ili bolestima, a jedna od značajnijih je celijakija gdje je primjena bezglutenske dijete osnova liječenja. Naš slučaj predstavlja mladu bolesnicu bez značajnih znakova ili simptoma osim povišene serumske amilaze otkrivene slučajnim probirom. Makroamilazemija je potvrđena bez znakova celijakije, a liječenje nije bilo potrebno.

Ključne riječi: **hiperamilazemija, laboratorijska dijagnostika, makroamilazemija**