UDK 616-008.9:577.152.3
COBISS.SR-ID 16549897

MAKROAMILAZEMIJA KAO RAZLOG HIPERAMILAZEMIJE U KLINIČKI NEJASNIM STANJIMA-PRIKAZ SLUČAJA

Zoran Joksimović (1), Dušan Bastać (2), Snežana Pavlović (3)

(1)INTERNISTIČKA ORDINACIJA "JOKSIMOVIĆ" BOR; (2) INTERNISTIČKA ORDINACIJA "DR BASTAĆ" ZAJEČAR; (3) SPECIJALISTIČKA ORDINACIJA ZA INTERNU MEDICINU " DR PAVLOVIĆ KARDIOLOGIJA" BEOGRAD

Sažetak: Makroamilazemija je retko stanje koje karakteriše povišen nivo amilaze u serumu usled postojanja složenih makromolekula amilaze koje bubrezi zbog njihove veličine ne mogu normalno da izlučuju. Radi se o benignom stanju koje je najčešće bez izraženih kliničkih simptoma i znakova. Prevalencija makroamilazemije u populaciji, iznosi između 1 i 2%. Glavni klinički značaj makroamilazemije je u tome što često predstavlja dijagnostički problem zahtevajući diferenciranje ovog stanja od drugih uzroka hiperamilazemije. Stoga je racionalno da se izbegne nepotrebna dijagnostika i lečenje, koji opterećuju i pacijenta i zdravstveni sistem. Makromalazemiju kao dijagnozu treba razmotriti kod svakog pacijenta sa povišenim nivoom aktivnosti amilaze u serumu kod koga je je nivo lipaze u serumu i amilaze u urinu normalan. Laboratorijska potvrda dijagnoze amilazemije počiva na testovima: elektroforeza ili test precipitacije polietilen glikola. U ovom radu je prikazan pacijent koji je zbog nespecifičnih tegoba od strane gastrointestinalnog trakta rutinski klinički obrađen i pri laboratorijskoj obradi seruma pacijenta je utvrđeno da ima povišene vrednosti amilaze. Dodatnom dijagnostikom nisu utvrđene organske bolesti pankreasa niti druge bolesti koje bi mogle da budu u vezi sa hiperamilazemijom a izračunavanjem odnosa bubrežnog klirensa amilaze i klirensa kreatinina koji je manji od 1% zaključujemo da se najverovatnije radi o makroamilazemiji. Specifično lečenje nije bilo potrebno. Pacijent dolazi na kontrolni pregled jednom na 6 meseci.

UVOD

Amilaza je amilolitički enzim koji pomaže varenje u crevima hidrolizujući polisaharide do manjih molekula. Kod čoveka se nalazi α -amilaza, koja kod zdravih individua potiče najviše iz pankreasa i pljuvačnih žlezda ali u klinički beznačajnim količinama i iz drugih organa (jetre, bubrega, jajovoda, mišića i dr.). Može se naći u dva osnovna oblika, takozvanih izoenzima- sintetisana u pankreasu (pankreasna ili P-izoamilaza) i nepankreasnog porekla (salivarna - pljuvačna ili S-izoamilaza). Uobičajeno je da se u krvi ili urinu nalaze niski nivoi amilaze. Ali ako se pankreas ili pljuvačne žlezde oštete nivo amilaze u krvi ili urinu raste. Serumska amilaza je povišena u najmanje 75% slučajeva pankreatitisa; Retko, serumska amilaza može biti normalna, čak i ako dođe do masivne nekroze pankreasa. [1]

Detaljni putevi metabolizma serumske amilaze još uvek nisu potpuno razjašnjeni. Smanjen metabolički klirens - bubrežna insuficijencija može biti razlog povišenog serumskog nivoa

amilaze. Osobe koje su imali nefrektomiju ili imaju bubrežnu insuficijenciju imaju prosečan nivo amilaze u serumu koji je 50% veći od zdravih pojedinaca. Stoga se može pretpostaviti da bubrezi igraju glavnu ulogu u metabolizmu amilaze. Međutim, bubrežni nije jedini organ koji je odgovoran za uklanjanje amilaze kod ljudi. Ekstranalni mehanizmi čišćenja amilaze nisu jasno definisani. Pošto se visoki nivoi amilaze u serumu primećuju i kod nekroze jetre i ciroze, smatra se da jetra igra ulogu u metabolizmu amilaze [2]. Zabeleženo je da mnoga stanja izazivaju hiperemilazemiju. Iako se obično pretpostavlja da je hiperamilazemija posledica oslobađanja amilaze u serumu od strane obolelog organa, precizan odnos između hiperemilazemije i patoloških stanja nije sasvim jasan. Hiperamilazemija je najčešće rezultat: pankreatitisa ili parotitisa, smanjenog metaboličkog klirensa amilaze ili amilaze oslobođene iz nekog oštećenog organa (van pankreasa i pljuvačnih žlezdi).

Akutni ili hronični pankreatitis je povezan sa povećanjem izoamilaze tipa P. Ostali razlozi za hiperamilazemiju koji su povezani sa pankreatitisom su pseudociste, trauma pankreasa i holecistolitijaza. Trauma pankreasa može biti rezultat tupih trauma, trbušnih ili retroperitonealnih operacija ili endoskopske retrogradne kanulacije pankreasnog kanala (ERCP). Kod pacijenata sa bolovima u trbuhu tipa bilijarnih kolika, trostruko povećanje nivoa amilaze u serumu koje se vrati u normalu u roku od 48-72 sata sugerise prolazak kamena kroz zajednički žučni kanal [3,4]. Parotitis usled infekta, traume ili zračenja je povezan sa povećanjem izoamilaze tipa S. Oštećenja pljuvačne žlezde može nastati i kao posledica hroničnog alkoholizma. Nivo amilaze u pljuvački je tri puta veći od normalnog kod 10% pacijenata lečenih od hroničnog alkoholizma. Diskutuje se i da je ova pojava kod alkoholičara posledica i/ili oštećenja jetre jer bolesti jetre (hepatitis ili ciroza) takođe pokazuje povišene nivoe izoamilaza tipa S i P [2].

Bolesti creva, (zapaljenjske bolesti creva, infarktmezenterijuma, ileus, peritonitis) mogu dovesti do povišenja nivoa pankreatične amilaze. Rupturirana ektopična trudnoća, ciste jajnika ili upala jajnika i jajovoda mogu rezultovati povišenom salivarnom izoamilazom. Proizvodnja ektopične amilaze je moguća u malignomima pluća, jajnika, pankreasa i debelog creva; feokromocitomu; timomu; multiplom mijelomu, karcinom dojke. Povećanje nivoa amilaze može se pojaviti postoperativno, nakon ekstrakorporalne cirkulacije ili ne-abdominalnih hirurških intervencija (npr. 30% pacijenata koji su podvrgnuti srčanom hirurškom posegu ima povišenu izoamilazu tipa S). Zabeleženi su retki slučajevi hipereamilazemije pri lečenju ciprofloksacinom. Ostali uzroci hiperamilazemije uključuju upale pluća, cerebralnu traumu, opekotine, aneurizme trbušne aorte, anoreksiju nervozu i kao i trovanje organofosfatnim jedinjenjima. [5,6] Povišeni enzimi pankreasa mogu se naći kod kritično povređenih pacijenata sa traumom čak i ako nema pravog pankreatitisa [1,2].

Makroamilazemija - Makroamilazemija je retko, benigno stanje u kojem se molekul

amilaze veže sa velikim složenim molekulama, smanjujući bubrežni klirens i produžavajući njegov poluživot. Prevalencija makroamilazemije u populaciji, iznosi između 1 i 2%. Oko 2% -5% pacijenata sa hiperamilazemijom ima makroamilazemiju. Makroamilazemiju, karakteriše hiperamilazemija ili povišeni nivo amilaze u serumu bez povišene amilaze u urinu i drugih kliničkih znakova ili simptoma. U makroamilazemiji, amilazu najčešće veže imunoglobulin, čineći je 4 puta većom nego što je to uobičajeno i bubrezi je sporo i otežano izlučuju, što rezultira visokim nivoom amilaze u serumu, ali normalnim nivoima u urinu (7-12). U većini slučajeva makromolekularna amilaza predstavlja kompleks normalne amilaze i imunoglobulina A ili G. Različiti radovi izveštavaju o različitim statistikama o incidenciji makroamilazemije. Ona je najčešće prisutna kod odraslih (češće muškog pola), mada su zabeleženi slučajevi kod dece i novorođenčadi. Povišen nivo amilaze u serumu je glavni kriterijum za dijagnozu pankreatitisa. Kada se radi o hiperamilazemiji kod makroamilazemije važno je na sto ranijem nivou obrade pacijenta prepoznati da li se radi o pankreatitisu ili benignoj hiperamilazemiji kako bi izbegli nepotrebnu dijagnostiku i lečenje, koji opterećuju i pacijenta i zdravstveni sistem. Ovo je važno između ostalog istoga što je glavno ograničenje upotrebe merenja serumske amilaze u dijagnostici stepena pankreatitisa nedostatak specifičnosti ovog testa [1,7,13].

Prihvaćen algoritam za zajedničku dijagnozu makroamilazemije, prilikom povišene serumske amilaze bez povišene amilaze u urinu, naknadno je testiranje na lipazu u serumu, što zajedno sa visokim nivoom amilaze obično sugerise pankreatitis [14]. Ako je serum lipaza normalna, mora se ispitati funkcija bubrega, jer će i abnormalni rad bubrega uzrokovati povišene nivoe amilaze. Onda kada zaključimo da je bubrežna funkcija normalna, treba izračunati bubrežni klirens amilaze u odnosu na klirens kreatinina - ACCR (Amylase-creatinine clearance ratio) prema formuli:

$$ACCR = \frac{\text{Amilaza u urinu}}{\text{Amilaza u serumu}} \times \frac{\text{Kreatinin u serumu}}{\text{Kreatinin u urinu}} \times 100$$

Normalni odnos ovih klirensa je između 3% i 5%, dok rezultat manji od 1% sugerira makroamilazemiju [13]. Konačni potvrđujući test je elektroforeza ili test precipitacije polietilen glikolom i hromatografija [14]. Kako se radi o metodama koje se rade u specijalizovanim laboratorijama i retko se koriste rutinski, većina se autora slaže da se izračunavanje ACCR odnosa može smatrati dijagnostičkim, mada postoje i određena neslaganja oko toga [7,13,15,16].

PRIKAZ SLUČAJA: Pacijent P.Ž. star 65 godine dolazi 10.7.2019. godine na gastroenterološki pregled zbog povremenog osećaja nadutosti u trbuhu i povišene serumske amilaze u laboratorijskim nalazima. Tegobe traju od oktobra 2018. godine i javljaju se povremeno, približno jednom u 7-10 dana, obično posle jela i popuste posle praznjenja creva. Negira teže i nasledne bolesti u ličnoj i porodičnoj anamnezi. Dobijao je simptomatsku terapiju (spazmolitici) koju je koristio po potrebi. Pri fizikalnom pregledu se konstatuje uredan objektivni nalaz. U laboratorijskim izveštajima koje pacijent donosi - kompletna krvna slika, sedimentacije eritrocita, i nivo C-reaktivnog proteina bili su u granicama referentnih vrednosti. Tumorski marker CA19/9 je bio 31,6U/ml (normalno do 37U/ml). Nivo amilaze u serumu bio je povišen - 235 IU / L (referentni opseg: do 100 IU / L). Ostali rezultati u biohemijskim parametrima, uključujući lipazu u serumu, azotne retente, aminotransferaze, bilirubine i serumsko gvožđe bili su normalni. Ultrazvuk i kompjuterska tomografija abdomena su pokazali normalan nalaz. Normalan je i nalaz UZ pregleda vrata (regija parotidnih žlezdi). Kontrolisani su laboratorijski parametri posle 3 meseca (30.10.2019. god.) uključujući brzinu sedimentacije eritrocita, CRP, lipazu, aminotransferaze, bilirubine i serumsko gvožđe kao i anti-tkivna transglutaminaza-IgA (anti-tTG-IgA). Svi su nalazi bili u granicama normale. Ostala je povišena serumska amilaza 197 IU/L. Amilaza u urinu je bila takođe u referentnim vrednostima 32 IU/L. Odredili smo kreatinin u serumu 75 umol/L i kreatinin u urinu 7003 umol radi izračunavanja ACCR. ACCR je 0,174.

Na osnovu kliničke slike obavljene dijagnostike i obračunatog ACCR zaključujemo da se vrlo verovatno radi o makroamilazemiji. Definitivna laboratorijska dijagnostika elektroforezom ili

testom precipitacije polietilen glikola nam nije bila dostupna a i pacijent nije bio motivisan za dodatnu dijagnostiku. Uz preporučenu dijetu dobijao je probiotsku terapiju i osmotski laksativ (makrogol) po potrebi. Pacijent je pregledan posle dva meseca (25.12.2019. godine). Bio je bez tegoba, klinički nalaz je bio uredan. Nivo amilaze u serumu je bio 210 IU/L, amilaza u urinu 45 IU/L. Zbog starosne dobi pacijenta predložena je donja digestivna endoskopija koju je pacijent odbio. Zakazan je kontrolni klinički sa novim nalazima laboratorije pregled i ultrazvučni pregled abdomena za 6 meseci. Kako je pacijent stariji od 50 godina predviđamo praćenje pacijenta još 1-2 godine da bi smo hiperamilazemiju definitivno proglasili benignom.

DISKUSIJA: Amilaza je enzim koji je odgovoran za razgradnju amilaze i drugih skroba tokom varenja. Postoji kao tri podtipa, gde se α - amilaza nalazi kod životinja, uključujući ljude, i ona je jedina od kliničke važnosti [6]. Iako je hiperamilazemija posebno povezana sa pankreatitisom, postoje i druga stanja i bolesti koja mogu da se pojave i kod hiperamilazemije, uključujući sialadenitis, plućnu bolest, ciste jajnika, rupturiranu ektopičnu trudnoću, traumatu trbuha, infarkt mezenterijuma, perforirani peptički ulkus, upala slepog creva, bubrežna insuficijencija, zauške i neka maligna stanja, a sve to bi zahtevalo dodatna ispitivanja, za razliku od makroamilazemije [1,2,6,8,12].

Iako je makroamilazemija uglavnom asimptomatska, često se dijagnostika ovog stanja počinje zbog bolova u trbuhu, uključujući i određivanje amilaze u serumu i urinu. Međutim bol u trbuhu nije simptom makroamilazemije. Najčešće je to samo slučajnost, a testiranje amilaze se često zahteva kada se pacijenti žale na bol u trbuhu. Prema jednoj hipotezi, koja nema potvrdu, bolovi u trbuhu i makroamilazemija otkrivaju se zajedno zbog taloženja molekula makroamilaze u pankreasu [13]. Problem u dijagnostici predstavlja moguća istovremena pojava makroamilazemije i drugih patoloških stanja poput ulceroznog kolitisa [17], Crohnove bolesti [18], hematoloških maligniteta [19,20], sistemskog lupus eritematozusa [21], reumatskog artritisa [22] ili celijakije [23,24,25]. Objavljeno je nekoliko slučajeva obolelih od celijakije sa makroamilazemijom kod kojih je došlo do normalizovanja amilazemije nakon lečenja dijetom bez glutena [26]. Opisana

je i indukovana makroamilazemija, što pokazuje jedno istraživanje gde je grupa ispitanika dobijala infuzije sa rastvorom hidroksietil skroba (HES), koji je volemični koloid korišćen u lečenju hipovolemije. Ispitivači su bili svi zdravi pojedinci koji su razvili hiperamilazemiju nakon infuzije sa HES rastvorom. Dokazano je da je hiperamilazemija posledica makroamilaze (kompleksa amilaze i HES). Kako su se molekuli HES-a raspadali, hiperamilazemija ili makroamilazemija su se same razrešavale. Ova studija je dokazala da makroamilazemija može da ima i jatrogenu indukciju [13].

U literaturi su opisani i drugi slučajevi asimptomatske hiperamilazemije, uključujući hroničnu nepatološku hiperamilazemiju pankreasnog porekla, etničku hiperamilazemiju i porodičnu hiperamilazemiju [27]. Teorija nastanka makro molekula amilaze se zasniva »disregulaciji« imunske tolerancije, koja se može pojaviti kod imunskih poremećaja [28]. Smatra se da postoji unakrsna reaktivnost ili na gluten ili druge antigene što dovodi do stvaranja autoantitela protiv pankreasne serumske amilaze na crevnom nivou. Na ovaj način se formiraju antitela, u većini slučajeva imunoglobulin A, retko imunoglobulin G, koji reaguju sa amilazom formirajući imune komplekse [29].

Skoro svi pacijenti koji imaju hiperamilazemiju prolaze skupe, duge, teške i često nepotrebno ponavljane dijagnostičke postupke. U jednoj studiji koja je pratila pacijente 4 godine 60,7% pacijenata je imalo dijagnozu hronični pankreatitis, 24,5% rekurentni pankreatitis a 13,7% je bilo bez posebne dijagnoze. Posle detaljne kliničke obrade (nivo Ca19-9 u serumu, ultrazvuk abdomena, kompjuterizovana tomografija i magnetna rezonanca, endoskopska retrogradna holangiopankreatografija i endoskopska ultrasonografija) u 35,2% ovih pacijenata je zaključeno da se radi o makroamilazemiji [30].

Da bi se izbegla neracionalna dijagnostika prilikom nalaza povišene serumske amilaze kod pacijenata bez itraženih kliničkih tegoba i simptoma, bez povišene amilaze u urinu i normalnog nivoa lipaze u serumu, treba ispitati funkciju bubrega i izračunati bubrežni klirens amilaze u odnosu na klirens kreatinina – ACCR, još u početku dijagnostičkog programa i proceniti potrebu za dodatnom dijagnostikom. U tom smislu je vrlo praktičan dijagnostički algoritam makroamilazemije koji su još 1989 god. predložili David LeVine i David Parrish [7].

ZAKLJUČAK:

Kod našeg pacijenta na osnovu kliničke slike, obavljene dijagnostike i obračunatog ACCR zaključujemo da se najverovatnije radi o makroamilazemiji. Ovi jednostavni i jeftini laboratorijski testovi i proračuni potvrdili su dijagnozu uprkos nedostatku potvrdnog laboratorijskog testa. (Definitivna dijagnostika elektroforezom ili testom precipitacije polietilen glikola nam nije bila dostupna a pacijent nije bio motivisan za dodatnu dijagnostiku). Uz preporučenu dijetu i terapiju pacijent je bio bez

tegoba. Zbog strosne dobi predložena je kolonoskopija koju je pacijent odbio. Zakazan je kontrolni klinički pregled i ultrazvučni pregled abdomena za 6 meseci.

Dijagnozu makroamilazemije treba razmotriti u diferencijalnoj dijagnozi pacijenata koji imaju trajno povišenu serumsku amilazu, ali ne pokazuju bilo kakve karakteristike pankreatitisa ili upale pljuvačnih žlezda. ACCR može biti brz i jeftin skrining test da se spreče nepotrebna dijagnostika i terapija.

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UDK 616-008.9:577.152.3
COBISS.SR-ID 16549897

MACROAMYLASEMIA AS A CAUSE OF HYPERAMYLASEMIA IN CLINICALLY UNCLEAR CONDITIONS-CASE REPORT

Zoran Joksimović (1), Dušan Bastać (2), Snežana Pavlović (3)

(1) INTERNIST PRACTICE "JOKSIMOVIĆ" BOR, (2) INTERNIST'S OFFICE "DR. BASTAĆ" ZAJEČAR; (3) SPECIALIST PRACTICE FOR INTERNAL MEDICINE "DR. PAVLOVIĆ CARDIOLOGY" BELGRADE

Abstract: Macroamylasemia is a rare condition characterized by elevated serum amylase levels due to the existence of macromolecules - complex amylase that cannot be secreted normally by the kidneys due to their size. It is a benign condition that is usually free of marked clinical symptoms and signs. The prevalence of macroamylasemia in the population is between 1 and 2%. The main clinical significance of macroamylasemia is that it is often a diagnostic problem because it requires differentiation of this condition from other causes of hyperamylasemia. Therefore, it is rational to avoid unnecessary diagnostics and treatment, which burden both the patient and the health system. Macromalaseemia as a diagnosis should be considered in any patient with elevated serum amylase activity in whom serum lipase and urine amylase levels are normal. Laboratory confirmation of the diagnosis of amylasemia rests on tests: electrophoresis or polyethylene glycol precipitation test. This paper presents a patient who has been routinely treated clinically due to non-specific gastrointestinal problems. During laboratory treatment, the patient's serum was found to have elevated amylase values. Additional diagnostics did not identify organic pancreatic diseases or other diseases that may be related to hyperamylasemia, and by calculating the ratio of renal amylase clearance to creatinine clearance of less than 1%, we conclude that it is most likely a macroamylasemia. Specific treatment was not required. The patient comes for a check-up once every 6 months.

INTRODUCTION:

Amylase is an amylolytic enzyme that helps digestion in the intestines by hydrolyzing polysaccharides to smaller molecules. In humans, there is α -amylase, which in healthy individuals originates mostly from the pancreas and salivary glands, but in clinically insignificant amounts from other organs (liver, kidneys, fallopian tubes, muscles, etc.). It can be found in two basic forms, the so-called isoenzymes - synthesized in the pancreas (pancreatic or P-isoamylase) and non-pancreatic origin (salivary - salivary or S-isoamylase). It is common to have low levels of amylase in the blood or urine. But if the pancreas or salivary glands are damaged, the level of amylase in the blood or urine increases. Serum amylase is elevated in at least 75% of cases of pancreatitis; Rarely, serum amylase may be normal, even if massive pancreatic necrosis occurs [1]

The detailed pathways of serum amylase metabolism have not yet been fully elucidated. Decreased metabolic clearance - renal failure may be the cause of elevated serum amylase

levels. People who have had a nephrectomy or have kidney failure have an average serum amylase level that is 50% higher than healthy individuals. Therefore, it can be assumed that the kidneys play a major role in amylase metabolism. However, the kidney is not the only organ responsible for removing amylase in humans. The extrinsic mechanisms of amylase clearance are not clearly defined. Since high serum amylase levels are also observed in liver necrosis and cirrhosis, the liver is thought to play a role in amylase metabolism [2] Many conditions have been reported to cause hyperamylasemia. Although hyperamylasemia is usually assumed to be a consequence of the release of serum amylase by the diseased organ, the precise relationship between hyperamylasemia and pathological conditions is not entirely clear. Hyperamylasemia is most often the result of: pancreatitis or mumps, decreased metabolic clearance of amylase or amylase released from a damaged organ (outside the pancreas and salivary glands).

Acute or chronic pancreatitis is associated with an increase in type P isoamylase. Other causes of hyperamylasemia associated with pancreatitis are pseudocysts, pancreatic trauma, and choledolithiasis. Pancreatic trauma can be the result of blunt trauma, abdominal or retroperitoneal surgery, or endoscopic retrograde pancreatic canal cannulation (ERCP). In patients with biliary colic-type abdominal pain, a threefold increase in serum amylase levels returns to normal within 48-72 hours. suggests the passage of a stone through the common bile duct [3,4]. Mumps due to infection, trauma or radiation is associated with an increase in type S isoamylase. Salivary gland damage can also occur as a consequence of chronic alcoholism. The level of amylase in saliva is three times higher than normal in 10% of patients treated for chronic alcoholism. It is also discussed that this phenomenon in alcoholics is a consequence of and / or liver damage because liver disease (hepatitis or cirrhosis) also shows elevated levels of isoamylases of type S and P [2].

Intestinal diseases (inflammatory bowel diseases, infarct mesentery, ileus, peritonitis) can lead to increased levels of pancreatic amylase. Ruptured ectopic pregnancy, ovarian cysts, or inflammation of the ovaries and fallopian tubes can result in elevated salivary isoamylase. Ectopic amylase production is possible in malignancies of the lungs, ovaries, pancreas, and colon; pheochromocytoma; team; multiple myeloma, breast cancer. Increases in amylase levels may occur postoperatively, after extracorporeal circulation or non-abdominal surgery (e.g., 30% of patients undergoing cardiac surgery have elevated type C isoamylase). Rare cases of hyperamylasemia have been reported with ciprofloxacin treatment. Other causes of hyperamylasemia include pneumonia, cerebral trauma, burns, abdominal aortic aneurysms, anorexia nervosa, and organophosphate poisoning. (5,6) Elevated pancreatic enzymes can be found in critically

injured patients with trauma even if there is no true pancreatitis [1,2].

Macroamylasemia - Macroamylasemia is a rare, benign condition in which the amylase molecule binds to large complex molecules, reducing renal clearance and prolonging its half-life. The prevalence of macroamylasemia in the population is between 1 and 2%. About 2% -5% of patients with hyperamylasemia have macroamylasemia. Macroamylasemia is characterized by hyperamylasemia or elevated serum amylase levels without elevated urine amylase and other clinical signs or symptoms. In macroamylasemia, amylase is most often bound by immunoglobulin, making it 4 times larger than usual and the kidneys excrete it slowly and with difficulty, resulting in high serum amylase levels but normal urine levels [7-12]. In most cases, macromolecular amylase is a complex of normal amylase and immunoglobulin A or G. Different papers report different statistics on the incidence of macroamylasemia. It is most often present in adults (more often males), although cases have been reported in children and newborns. Elevated serum amylase levels are the main criterion for the diagnosis of pancreatitis. health system. This is important, among other things, because the main limitation of the use of serum amylase measurements in the diagnosis of the degree of pancreatitis is the lack of specificity of this test [1,7,13].

An accepted algorithm for the joint diagnosis of macroamylasemia, in elevated serum amylase without elevated urinary amylase, is subsequent serum lipase testing, which together with high amylase levels usually suggests pancreatitis [14]. If serum lipase is normal, renal function must be examined. because abnormal kidney function will also cause elevated amylase levels. Then when we conclude that renal function is normal, we should calculate the renal amylase clearance in relation to creatinine clearance - ACCR (Amylase-creatinine clearance ratio) according to the formula:

$$ACCR = \frac{\text{amylase in urine}}{\text{serum amylase}} \times \frac{\text{serum creatinine}}{\text{creatinine in urine}} \times 100$$

The normal ratio of these clearance is between 3% and 5%, while a result of less than 1% suggests macroamylasemia [13]. The final

confirmatory test is electrophoresis or polyethylene glycol precipitation test and chromatography [14]. As these are methods

used in specialized laboratories and are rarely used routinely, most authors agree that the calculation of ACCR ratios can be considered diagnostic, although there are some discrepancies that [7,13,15,16].

CASE REPORT: Patient P.Ž. The 65-year-old comes for a gastroenterological examination on July 10, 2019. due to an occasional feeling of bloating in the abdomen and elevated serum amylase in the laboratory findings. The problems last from October 2018 and occur occasionally, approximately once in 7-10 days, usually after meals and discounts after bowel movements. It denies severe and hereditary diseases in personal and family history. He received symptomatic therapy (spasmolytics) which he used as needed. During the physical examination, an orderly objective finding is ascertained. In the laboratory reports that the patient brings - complete blood count, erythrocyte sedimentation rate, and C-reactive protein level were within the reference values. Tumor marker CA19 / 9 was 31.6U / ml (normally up to 37 U/ml). Serum amylase levels were elevated - 235 IU / L (reference range: up to 100 IU / L). Other results in biochemical parameters, including serum lipase, nitrogen retention, aminotransferases, bilirubin, and serum iron were normal. Ultrasound and computed tomography of the abdomen showed a normal finding. An ultrasound examination of the neck (parotid gland region) is also normal. Laboratory parameters were monitored after 3 months (30.10.2019) including erythrocyte sedimentation rate, CRP, lipase, aminotransferase, bilirubin and serum iron as well as anti-tissue transglutaminase-IgA (anti-tTG-IgA). All findings were within normal limits. Elevated serum amylase remained 197 IU / l. Urine amylase was also at reference values of 32 IU / l. We determined serum creatinine 75 umol / L and urine creatinine 7003 umol to calculate ACCR. The ACCR is 0.174.

Based on the clinical picture of the performed diagnosis and calculated ACCR, we conclude that it is very likely macroamylasemia. Definitive laboratory diagnosis by electrophoresis or polyethylene glycol precipitation test was not available to us and the patient was not motivated for additional diagnostics. (macrogol) as needed. The patient was examined after two months (December 25, 2019). He was without

problems, the clinical findings were orderly. Serum amylase levels were 210 IU / L, urine amylase 45 IU / L. Due to the patient's advanced age, lower digestive endoscopy was suggested, which the patient refused. A clinical control with new laboratory findings and an ultrasound examination of the abdomen is scheduled for 6 months. As the patient is older than 50, we anticipate monitoring the patient for another 1-2 years in order to definitely declare hypermilasemia benign.

DISCUSSION:

Amylase is an enzyme 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 particularly associated with pancreatitis, there are other conditions and diseases that can occur with hyperamylasemia, including sialadenitis, lung disease, ovarian cysts, ruptured ectopic pregnancy, abdominal trauma, mesenteric infarction, perforated peptic ulcer, appendicitis, renal failure, mumps, and some malignancies, all of which would require additional testing, unlike macroamylasemia [1,2,6,8,12].

Although macroamylasemia is mostly asymptomatic, diagnosis of this condition often begins with abdominal pain, including determination of serum and urine amylase. However, abdominal pain is not a symptom of macroamylasemia. It is usually just a coincidence, and amylase testing is often required when patients complain. to abdominal pain. According to one hypothesis, which has no confirmation, abdominal pain and macroamylasemia are detected together due to the deposition of macroamylase molecules in the pancreas [13], hematological malignancies [19,20] of systemic lupus erythematosus [21], rheumatoid arthritis [22] or celiac disease [23,24,25]. Several cases of celiac disease with macroamylasemia have been reported in which amylasemia has returned to normal after treatment with [26] Induced macroamylasemia has also been described, as shown by a study in which a group of subjects received infusions with a solution of hydroxyethyl starch (HES), a volemic colloid used in the treatment of hypovolaemia. with HES solution Hyperamylasemia has been shown to be due to

macroamylase amylase complex and HES). As HES molecules disintegrated, hyperamylasemia or macroamylasemia resolved on their own. This study demonstrated that macroamylasemia may also have iatrogenic induction [13].

Other cases of asymptomatic hyperamylasemia have been reported in the literature, including chronic nonpathological hyperamylasemia of pancreatic origin, ethnic hyperamylasemia, and familial hyperamylasemia [27].

The theory of the formation of macro molecules of amylase is based on the "dysregulation" of immune tolerance, which can occur in immune disorders [28]. Cross-reactivity to either gluten or other antigens is thought to lead to the formation of autoantibodies against pancreatic serum amylase at the intestinal level. In this way, antibodies are formed, in most cases immunoglobulin A, rarely immunoglobulin G, which react with amylase to form immune complexes [29].

Almost all patients who have hyperamylasemia undergo expensive, long, difficult and often

unnecessarily repeated diagnostic procedures. In one study that followed patients for 4 years, 60.7% of patients were diagnosed with chronic pancreatitis, 24.5% with recurrent pancreatitis and 13.7% had no specific diagnosis. After detailed clinical processing (serum Ca19-9 level, ultrasound) abdomen, computed tomography and magnetic resonance imaging, endoscopic retrograde cholangiopancreatography and endoscopic ultrasonography) in 35.2% of these patients it was concluded that it was macroamylasemia [30].

To avoid irrational diagnosis of elevated serum amylase in patients without clinical symptoms and symptoms, without elevated urinary amylase and normal serum lipase levels, renal function should be examined and renal amylase clearance calculated relative to creatinine clearance - ACCR at the beginning of the diagnostic program and assess the need for additional diagnostics. In that sense, the diagnostic algorithm of macroamylasemia, which dates back to 1989, is very practical. proposed by David LeVine and David Parrish [7].

Conclusion: In our patient, based on the clinical picture, performed diagnostics and calculated ACCR, we conclude that it is most likely

macroamylasemia. These simple and inexpensive laboratory tests and calculations confirmed the diagnosis despite the lack of a

confirmatory laboratory test (Definitive diagnosis by electrophoresis or polyethylene glycol precipitation test was not available to us and the patient was not motivated for additional diagnosis). With the recommended diet and therapy, the patient was without any problems. Due to age, a colonoscopy was suggested, which the patient refused. A control clinical examination and ultrasound examination of the abdomen are scheduled for 6 months.

The diagnosis of macroamylasemia should be considered in the differential diagnosis of patients who have permanently elevated serum amylase, but do not show any characteristics of pancreatitis or inflammation of the salivary glands. ACCR can be a quick and inexpensive screening test to prevent unnecessary diagnosis and therapy.

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