REVIEW ARTICLE

Persistent Chronic Hyperamylasemia: Clinical Interpretation and Diagnostic Approach

Ingrid Borovickova[1], Nikita R Bhatt[2], Gerard P Boran[1], Paul F Ridgway[2]

Departments of [1]Biochemistry and [2]Surgery, Tallaght Hospital, Adelaide and Meath Hospital, Tallaght, Dublin 24, Ireland

ABSTRACT

Amylase is often requested in a patient population with a low pre-test probability of acute pancreatitis in the setting of nonspecific symptoms. Hyperamylasemia that persists for weeks or months without apparent cause is often challenging and not uncommon in clinical practice. Chronic asymptomatic hyperamylasemia, based on ethnic and age appropriate reference range, can be further classified into nonpancreatic hyperamylasemia and pancreatic hyperamylasemia that is usually associated with elevated lipase activity. The aim of this article was to outline the aetiology of chronic hyperamylasemia to help clinicians choose appropriate further investigations and reach a prompt diagnosis. We also propose a diagnostic algorithm for patients with chronic hyperamylasemia.

INTRODUCTION

Serum amylase is the most frequently used biochemical marker for acute pancreatitis because of its wide availability and sensitivity. Although raised amylase activity is a sensitive test for acute pancreatitis, it is not specific for this condition and hyperamylasemia has been reported to occur in a myriad of other pancreatic and non-pancreatic conditions **(Table 1)** [1].

It is this lack of specificity and wide availability that poses problems for clinicians confronted with interpreting raised amylase activity unrelated to acute pancreatitis. It is often requested in a population with a low pre-test probability as part of a general laboratory workup or in the setting of nonspecific symptoms.

It was shown that among 1000 consecutive ED patients with abdominal pain, amylase activity was obtained in 39%, but only 3.9% of the individuals were eventually diagnosed with pancreatitis [2].

Hyperamylasemia that persists for weeks or months without apparent cause is often challenging and not uncommon in clinical practice [3, 4, 5, 6].

Hyperamylasemia to the order of less than three times the normal upper reference limit has been reported in approximately 2.6% of hospitalised patients with non-pancreatic disease [7].

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Correspondence Paul F Ridgway
Department of Surgery
Adelaide and Meath Hospital, Tallaght
Dublin 24, Ireland
Phone + 0035314142211
E-mail ridgwayp@tcd.ie

If such patients are asymptomatic or present with nonspecific abdominal pain, which may have been the precipitating factor in initiating the workup [8] they might undergo unnecessary and sometimes invasive investigations.

The aim of this review article was to outline the etiology of chronic hyperamylasemia to guide clinicians chose appropriate further investigations and reach a prompt diagnosis. We also propose a diagnostic algorithm for the patients with chronic hyperamylasemia.

METHODS

A preliminary search of the literature on chronic hyperamylasemia was undertaken. MEDLINE (PubMed) and Google Scholar were searched to identify eligible studies. Search terms included “chronic hyperamylasemia”, “isoenzymes”, “salivary”, “pancreatic”, “amylase”, “macroamylase” in various combinations with relevant BOOLEAN operators. Only human studies in adults were considered. Observational prospective and retrospective case controlled trials, cohort and cross-sectional studies, case series and case reports were included. Animal studies were excluded. There were no limitations on gender or ethnicity of study population. Chronic hyperamylasemia was defined as a serum or plasma amylase activity above the reference range present for three weeks or longer. There were no restrictions on dates, language or publication status. The list of titles and abstracts was screened by one reviewer against the inclusion and exclusion criteria and excluded as appropriate. Full-text articles were retrieved and reviewed against the inclusion criteria by two independent reviewers. The primary outcome studied was etiology of chronic hyperamylasemia to clinically investigate this condition. The secondary

Table 1. Etiology of hyperamylasemia.

Hyperamylasemia associated with abdominal pain
Pancreatic disorders (P-type)
Pancreatitis of any aetiology: alcohol, biliary tract disease, trauma, hyperlipidemia
Complications of acute pancreatitis: pancreatic abscess, pseudocyst, ascites, pleural effusion
Pancreatic trauma (blunt trauma, abdominal/retroperitoneal surgery, ERCP)
Pancreatic carcinoma
Non-pancreatic gastrointestinal tract/vascular conditions (P-type)
Acute cholecystitis, choledocholithiasis
Gastritis, duodenitis, gastroenteritis, peptic ulcer
Inflammatory bowel disease
Intestinal obstruction
Peritonitis
Dissecting/Ruptured abdominal aortic aneurysm
Mesenteric infarction
Abdominal Trauma
Non-pancreatic genitourinary conditions (S-type)
Ureteric calculi
Endometriosis, salpingitis
Ectopic, ruptured tubal pregnancy
Hyperamylasemia associated with salivary gland disorders (S-type)
Chronic alcoholism
Anorexia nervosa/Bulimia
Duct obstruction/calculi
Sjogren's syndrome
Mumps
Trauma, surgery
Injection of contrast medium into salivary ducts for sialography
Miscellaneous causes of hyperamylasemia (S-type, P-type or mixed)
Tumors: carcinoma of lung, ovary, breast, renal cell, colon, thymoma, multiple myeloma, haematologic malignancies, phaeochromocytoma
Renal failure
Liver disease: hepatitis, liver cirrhosis, hepatocellular carcinoma
Acute alcoholic abuse
Diabetic ketoacidosis and non-ketotic acidosis
Post-surgery: pancreatic, abdominal, hepatic, biliary, cardiovascular, post-ERCP, liver transplantation
Macroamylasemia
Acute MI
AIDS
Acute porphyria
GSD I
Medication: Anti-HIV (Atazanavir, Cidofovir, Enfuvirtide, Foscarnet, Indinavir, Lamivudine, Zidovudine), Azathioprine, Clozapine, Cyclosporine, Didanosine, Ephedrine, oral contraceptives, Paracetamol, Pentamidine, Propofol, Ritodrine, Roxithromycin, steroids, Tamoxifen

outcome was to propose a diagnsotic algorithm for chronic hypermylasemia.

DISCUSSION

The initial search provided articles, we included 87 eligible studies in this review. The article types included were 61 review articles, 14 original articles, 8 case reports and 4 textbook articles. The results are discussed in three sections: biochemistry of hyperamylasemia, differential diagnosis of hyperamylasemia including pancreatic and non-pancreatic causes and finally a diagnostic algorithm for chronic hyperamylasemia.

DEFINITION OF CHRONIC HYPERAMYLASEMIA

The term chronic is ill defined and we propose to define chronic hyperamylasemia as a persistently raised serum or plasma amylase activity for three weeks and longer, based on the prospective and retrospective cohort and cross-sectional observational and case control studies [3, 4, 5, 9, 10, 11, 12, 13, 14, 15, 16].

The decision limit acted upon is also not well defined. Unlike acute pancreatitis where the decision limit proposed is usually ≥3x the upper limit of normal [17] chronic hyperamylasemia can be defined as a serum or plasma activity above the upper limit of a method-specific reference range (using the IFCC recommended method at 37oC, the serum reference interval in adults is 28–100 U/L) acknowledging that 2.5% of the healthy population would also fall in this category if a 97.5 percentile upper limit of normal is used.

Biochemistry of Amylase

Human serum contains two amylase isoenzymes, pancreatic and salivary type accounting for 45-50% and 50-60% of total amylase activity respectively [18].

Pancreatic amylase is specific to the pancreas, synthesized by acinar cells and secreted into the intestinal tract [4]. Salivary amylase, predominantly produced in salivary glands to initiate hydrolysis of starches while the food is still in the mouth and esophagus, can also originate from other sites (genitourinary epithelium, lacrimal glands, sweat, breast milk, amniotic fluid, lungs, striated muscle, adipose tissue, some neoplasms), although this extra-salivary production contributes little to the total plasma amylase activity in healthy subjects [19].

The isoenzymes undergo posttranslational modification to form a number of isoforms that have been separated in both serum and urine using isoelectric focusing or electrophoresis. Molecular weights of this mixture of isoenzymes and isoforms range from 54 to 62 kDa, hence the enzyme is small enough to pass through the glomeruli of the kidneys. It is only partially reabsorbed by the renal tubular system and approximately 25% of serum amylase activity is excreted by the kidney [20, 21]. The great proportion of circulating enzyme is removed by the reticulo-endothelial system, with the liver suggested to be a major organ for amylase removal [22, 23]. Thus, individuals with renal insufficiency or nephrectomy have average serum amylase activity 50% higher than healthy individuals and raised amylase activity has also been observed in hepatic cirrhosis and necrosis of the liver [24]. Reduced clearance of amylase due to liver cirrhosis or renal insufficiency should be excluded before submitting the patient for further investigations.

Pre-analytical factors considered in chronic hyperamylasemia: Ethno-racial differences in mean serum amylase activity have been recognised to influence serum amylase activity. Tsianos et al. reported that serum amylase activity was highest in West Indians, intermediate

in Asians and lowest in Caucasians and 32% of Asians and 50% of West Indians had total amylase activity above the upper limit of the reference range from Britons [25]. Such a finding could lead to unnecessary pancreatic investigation in these ethnic groups unless the appropriate reference range is used. Ueda et al. reported that serum total and isoamylase activity is higher in the elderly, in both men and women, most likely due to age related decline of renal function [26]. Beyond the eight decade, the upper level of the normal range rises by approximately 40% [27].

DIFFERENTIAL DIAGNOSIS OF CHRONIC HYPER-AMYLASEMIA

In the absence of abdominal pain, amylase activity is usually mildly to moderately elevated. Based on the amylase isoenzyme patterns, chronic hyperamylasemia can be classified as pancreatic and non-pancreatic **(Figure 1)**. The main observational studies of subjects with chronic hyperamylasemia and findings of amylase patterns are summarised in **Table 2** [3, 4, 5, 10, 13].

Chronic Pancreatic Hyperamylasemia

Chronic pancreatic hyperamylasemia, characterised by elevated pancreatic amylase, warrants pancreatic exploration by laboratory and imaging techniques and a careful follow-up [9, 28].

Although continued activity of pancreatitis, a pseudocyst, or pancreatic ascites accounts for some of the cases of persistent hyperamylasemia, in many subjects diagnostic evaluation fails to reveal pancreatic disease.

Pancreatic hyperamylasemia in subjects without abdominal symptoms can be associated with celiac disease, viral hepatitis or dyslipidemia [23].

Rarely, an apparently benign pancreatic hyperamylasemia can be the first sign of pancreatic cancer (intraductal mucin-producing, adenocarcinoma and others [23, 29]. Intraductal papillary mucinous tumours may occasionally manifest with pancreatic asymptomatic hyperamylasemia, likely due to a partial or total occlusion of the main pancreatic duct or secondary branches by mucinous material [29].

All subjects with chronic pancreatic hyperamylasemia especially those over 50 years of age [23], should therefore be followed for 1-2 years follow-up before the finding can be considered benign [23]. Careful clinical evaluation is important to exclude the role of some drugs such as anti HIV medication, azathioprine, clozapine, steroids, paracetamol, cyclosporine or systematic disease including renal failure, liver disease, HIV or tumors **(Table 1)**, although the latter is less likely in an asymptomatic individual. Clinical

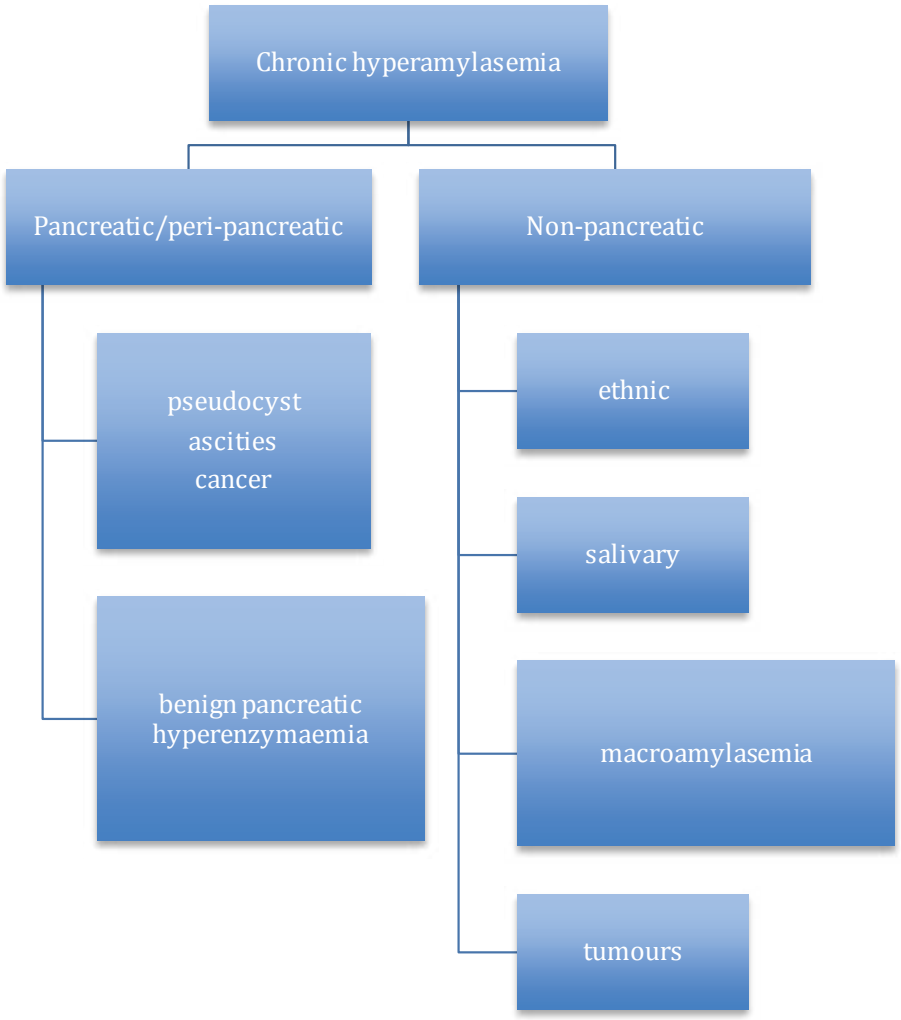
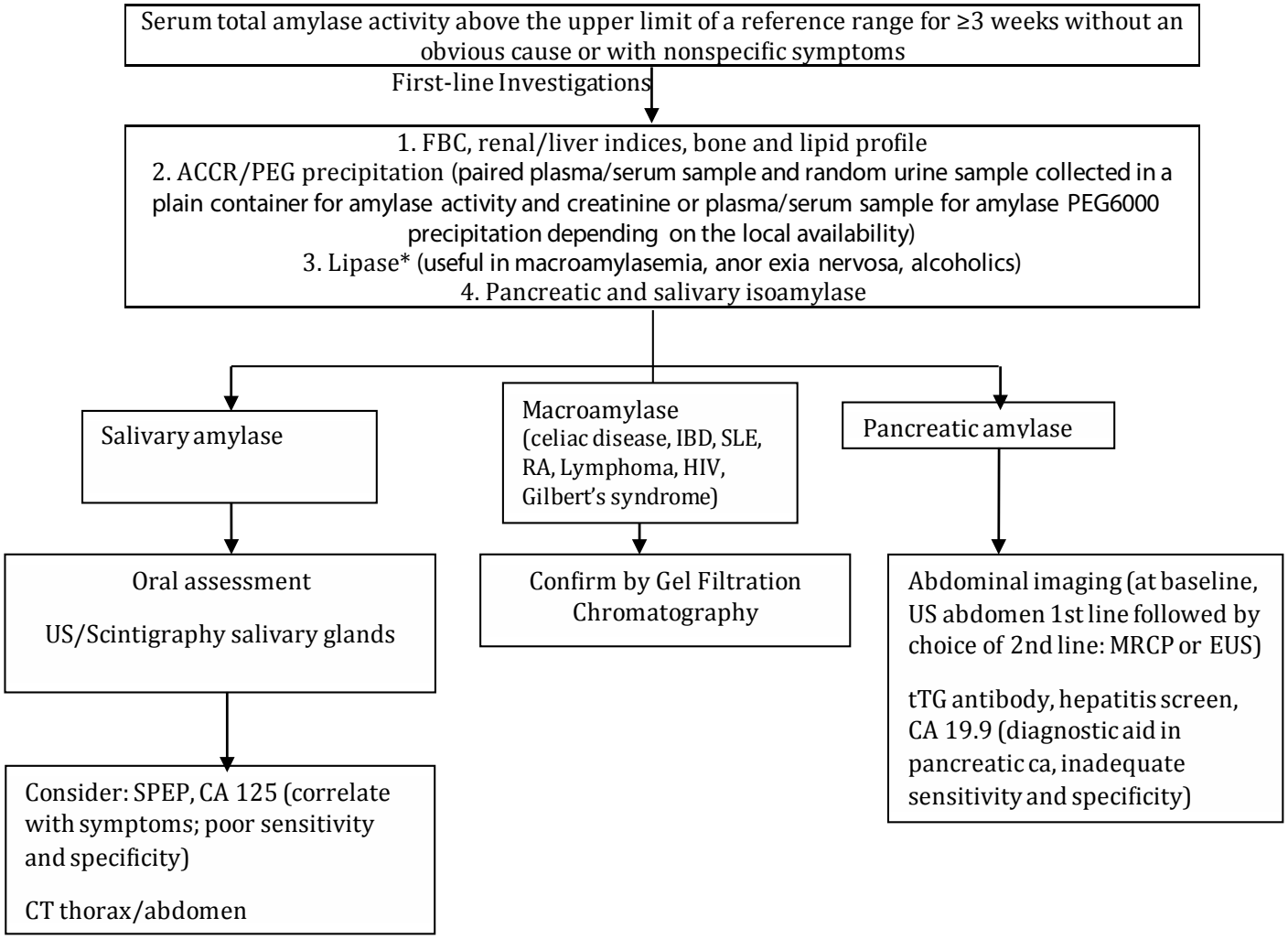


Figure 1. Differential diagnosis of hyperamylasemia.

Figure 2. A suggested diagnostic approach to persistent hyperamylasemia.



ACCR, amylase creatinine clearance ratio; FBC, full blood count; IBD, inflammatory bowel disease; PEG, polyethylene glycol; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; SPEP, serum protein electrophoresis; tTG, tissue transglutaminase activity; US, ultrasound.

*Serum lipase can be raised in a variety of non-pancreatic conditions along with amylase. Lipase analysis is particularly useful in macroamyloasemia and conditions affecting salivary glands (in both cases serum lipase activity will be normal).

history and examination, routine laboratory investigations, abdominal ultrasonography and computed tomography are sufficient in majority of cases to exclude pancreatic disease.

Benign pancreatic hyperenzymemia: Benign pancreatic hyperenzymemia, a syndrome first described by Gullo, is characterized by raised serum amylase, pancreatic isoamylase, lipase and trypsin activities in asymptomatic subjects with no evidence of pancreatic disease by imaging [11, 12]. The syndrome occurs sporadically or in a familial form and amylase activity fluctuates significantly with occasional transient normalization in some cases. CFTR, SPINK1 and PRSS1 gene mutations do not seem to have a role in the etiology of the condition and benign pancreatic hyperenzymemia cannot be explained by mutations in genes whose variants are known to be associated with pancreatitis or by mutations in other *PRSS1/SPINK1* genes. Pezzilli et al found that about one-third of patients with chronic nonpathological pancreatic hyperenzymemia had abnormally high fecal calprotectin concentrations [15] and they recommended to evaluate the finding for the possible link between intestinal ecology and pancreatic enzyme alteration.

In 90-95% of the cases studied, serum levels of all pancreatic enzymes were elevated; in the remaining 5-10% only amylase or rarely only lipase levels were increased. Gullo studied these individuals for a considerable period of time (range 5.3-17.2 years, average 7.3 years).

The fluctuations of the enzymes were however not related to the reference change value, incorporating analytical and biological variation, when comparing serial test results and to the relation of phlebotomy to meals.

In individuals with persistently high levels of pancreatic isoamylase but no symptoms or signs of pancreatic disease, MRCP findings were reported in five observational studies [11, 12, 14, 15, 16, 24]. Overall the findings were abnormal in 34.6% (9.5%-57.4%) subjects demonstrating ductal dilatation and/or irregularity, pancreas divisum, small cyst/s and other abnormalities. As noted by Mariani, [28] the association between asymptomatic hyperamylasemia and pancreatic morphological abnormalities was likely coincidental, supported by several observations such as no evidence of duct obstruction with the normal outflow of pancreatic juice through the minor papilla under secretin stimulation, the long-standing increase of pancreatic

Table 2. Studies of subjects with persistent hyperamylasemia and findings of amylase patterns.

Study	Subjects	Duration§ of raised amylase	Macro amylase (%)	Salivary amylase (%)	Pancreatic amylase (%)	Mixed pattern (%)
Levitt et al. 1980	28	≥ 4/52	8 (28.6)	14 (50)	-	6 (21.4)
Warshaw et al. 1988	117	3-48/52	7 (6)	11 (9.4)	21 (17.9)	75 (64.1)*
Ventrucci et al. 1991	25	≥4/52 (mean 3 years)	3 (12)	16 (64)	3 (12)	2 (8)**
Gullo et al. 1996	47	12-10 years (mean12.6 months)	8 (17)	11 (23.4)	19 (40.4)	9 (19.1)
Gallucci et al. 2010	51	-	18 (35.3)	13 (25.5)	20 (39.2)	
Total	268		44 (16.4)	65 (24.3)	63 (23.5)	92 (34.3)

§ interval between the first detection of raised amylase and entry into the study

*old amylase related to prolonged handling and transport of the sera from other hospitals seen in 3 individuals

**normal salivary and pancreatic amylase seen in 1 individual

enzymes in some cases for more than 20-30 years or the fluctuations in enzyme activity. More controlled trials are needed to clarify whether pancreatic morphological abnormalities in asymptomatic subjects with raised pancreatic enzymes are more frequent than in controls and whether there is a causal relationship between hyperenzymemia and these pancreatic abnormalities.

Non-Pancreatic Hyperamylasemia

Warshaw et al. showed that nonpancreatic causes of hyperamylasemia were demonstrated in the majority of the patients with raised serum amylase activity at least twice normal for a minimum of 3 weeks. Macroamylasemia accounted for only 6% and salivary hyperamylasemia for 9% of the cases. The biggest single group (64%) had a normal distribution of isoamylases albeit at unusually high concentrations of no pathological significance [28]. Other studies [5, 10, 11, 13] **(Table 2)** showed different prevalence of pancreatic and nonpancreatic hyperamylasemia. These differences might be partly due to different patient selection process criteria, the type of institution where the study was undertaken (tertiary referral centre versus general hospital) or the extent of investigations performed.

Salivary hyperamylasemia: Salivary hyperamylasemia is diagnosed based on increased total plasma amylase activity and its salivary isoform of greater 60% of the total amylase activity.

Salivary glands disorders: Damage of salivary glands, leading to salivary hyperamylasemia has been seen in trauma or surgery to the salivary gland, radiation to the neck area involving the parotid gland and subsequently causing duct obstruction, or calculi of the salivary glands [30, 31, 32]. Another cause of subclinical damage to the salivary gland is chronic alcoholism and anorexia nervosa. Salivary amylase activity is 3 times higher than normal in 10% of patients with alcoholism; this may also be related to chronic liver disease [22].

Anorexia nervosa/Bulimia: Hyperamylasemia in anorexia nervosa is associated with vomiting and indeed the finding of raised salivary amylase may provide a clue to concealed vomiting. However pancreatitis may occur in these patients particularly during the course of refeeding and so measurement of plasma lipase and/or amylase isoenzymes may be justified to differentiate pancreatitis from salivary hyperamylasemia [28, 33, 34, 35].

Tumors: Hyperamylasemia may be associated with various tumors caused by either an ectopic production of the enzyme by the tumors or perhaps inflammatory response by the tumor cells resulting in marked release of the enzyme normally produced in these tissues into the blood stream [9, 36]. The raised isoenzyme is almost exclusively salivary type in ovarian, lung cancer, multiple myeloma and phaeochromocytoma [37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49].

Amylase-producing tumours of the lung are rare and may comprise in total only 1–3% of all lung carcinomas and, in these cases, the salivary amylase isotype is generally found [49, 50, 51, 52].

Amylase producing lung carcinomas are mostly adenocarcinomas but hyperamylasemia has also been reported in small cell carcinoma also. Amylase activity has been suggested as a useful tumour marker for monitoring the patient's treatment in amylase-producing lung carcinoma [50, 51, 52, 53, 54].

Zakrezewska and Pietrynczak reported that 39% of patients with ovarian carcinoma had hyperamylasaemia which is salivary-type dominant and that salivary amylase may be useful in the evaluation of radiotherapy effectiveness in this context [18, 54].

Ovarian carcinomas are also associated with hyperamylasemia [55, 56]. Kawakita et al. assessed plasma amylase activity, CA 19-9 and CA125 levels on 228 Japanese women undergoing salpingo-oophorectomy, measured prior to surgery [36]. The investigators showed that those with ovarian carcinoma had a significantly higher incidence of hyperamylasaemia when compared with the group of women with benign ovarian tumours (21.4% *vs.* 6.3%; OR 4.03 and after adjusting for age, the OR was 3.48). Serum amylase activity was significantly higher in patients with serous adenocarcinoma than patients with other types of ovarian carcinoma. Interestingly there was no demonstrable correlation between amylase and CA125 and negative correlation with CA19-9 in patients with ovarian Ca. The limitation of the study was its retrospective design, relatively small study group, short observational period and women with various stages of carcinoma.

Serum amylase activity may be increased in some patients with multiple myeloma although the actual prevalence of hyperamylasaemia in multiple myeloma remains unknown. Increased amylase activity is due to salivary-type hyperamylasemia in the majority of the patients (sialyl salivary type) [37].

A common feature of the myeloma cell lines associated with hyperamylasemia was a translocation of chromosome 1, which harbours the gene for amylase [39, 46]. The link does not appear to be immunoglobulin class-specific [45]. The onset of hyperamylasemia was reported to be associated with a rapid disease progression, extensive bone destruction and increase mortality, hence serum amylase activity may be a useful prognostic 'tumour marker' (the activity decreases in response to treatment and increases at times of relapse) in patients with multiple myeloma [41, 43].

Some patients with phaechromocytoma/paraganglioma were found to have hyperamylasemia, usually the salivary isotype. Here, hyperamylasemia may be related to the hypertensive crisis and vasoconstriction leading to tissue hypoxia rather than being a result of tumour secretion and is often transient [38, 48, 49].

Miscellaneous conditions associated with raised salivary amylase: Salivary-type hyperamylasemia has also been observed in various conditions without salivary gland disorders, such as diabetic ketoacidosis, pneumonia and postoperative states in a wide variety of surgical interventions including extra abdominal procedures such as post coronary bypasss [34].

Mixed salivary and pancreatic hyperamylasemia: As shown previously a normal distribution of isoamylases albeit at unusually high concentrations is of no pathological significance [46].

Macroamylasemia: Some studies have found that chronic hyperamylasemia is often unrelated to the pancreas and emphasized the importance of either salivary-type hyperamylasemia or macroamylasemia, whose clinical significance is poorly understood. Macroamylasemia can be detected in approximately one in 20 individuals with hyperamylasemia [57] and can account for as much as 28% of chronic otherwise unexplained hyperamylasemia.

Macroamylase is a complex between ordinary amylase (usually salivary type) and IgA or IgG in 70% and 30% of cases respectively [35].

Due to its high molecular weight (greater than 200 kDa) and size, it is not filtered through the glomeruli of the kidneys and is retained in the plasma where its presence usually increases plasma amylase activity twofold to eightfold above the upper reference limit. It can be found in 1% of patients with an amylase in the reference range, 5% of patients with an elevated amylase and 13% of HIV positive patients with an elevated amylase [35].

It is usually a benign chronic finding with no associated clinical symptoms although it may be transient. Macroamylasemia can be associated with some autoimmune conditions such as celiac disease, ulcerative colitis and rheumatoid arthritis as well as lymphoma, HIV infection or after administration of hydroxyethyl starch [51, 58, 59]**.** It is important to identify macroamylase in order to avoid unnecessary invasive and expensive tests.

A finding of persistently raised total amylase and normal lipase should raise the possibility of macroamylasemia. Amylase creatinine clearance ratio (ACCR) or polyethylene glycol (PEG) precipitation are useful screening tests for macroamylase. ACCR is easy to calculate from paired random urine and serum amylase and creatinine measurements. Normal ACCR is 1.6% [57]. Reduced ACCR of less than 1% is suggestive of macroamylasaemia but each laboratory should investigate the transferability of the expected values to its own patient population and if necessary determine its own reference ranges.

Precipitation of the complex by a PEG 6000 solution is an alternative and easy to perform screening test although less available in routine laboratories. Residual amylase activity of less than 30% in the supernatant is indicative of macroamylasemia [60]. The confirmatory gold standard test for the presence of macroamylasemia is a gel filtration chromatography which has the ability to exclude a coexistence of macroamylase and true hyperamylasemia and is performed in specialised laboratories.

PROPOSED DIAGNOSTIC ALGORITHM

Our proposed diagnostic algorithm of chronic hyperamylasemia is based on the best available information from the review of the topic and the expert opinion of the reviewers **(Figure 2)**.

Laboratory Testing In a Proposed Diagnostic Algorithm

Full blood count and routine biochemistry are first line investigations to narrow down the differential diagnosis. Because of the relatively common occurrence of macroamylasemia and the ease, availability and affordability of the screening tests, notably ACCR or PEG precipitation, macroamylasemia should be excluded first to prevent unnecessary investigations.

Serum lipase measurement can be raised in individuals with abdominal disorders unrelated to pancreas [23, 61] and so is of limited additional benefit. Its lack of availability and additional cost is the reason why most laboratories continue to measure amylase activity as a first line test. Serum lipase can be useful where another condition that causes an increase in S-type amylase is also present such as anorexia nervosa, alcohol abuse or salivary gland pathology.

Amylase P-type and S-type isoenzymes can be determined by using different methodologies however, only the methods based on selective inhibition by monoclonal antibodies have shown sufficient precision, reliability, practicability, and analytical speed to allow reliable measurement of P-type amylase. A commercially available assay that uses the synergistic action of two

immunoinhibitory monoclonal antibodies to S-type amylase is available [62].

The uninhibited P-type amylase activity is then measured. False positive P-type amylase results have been reported in subjects with macroamylasaemia, as the complex diminishes the ability of monoclonal antibodies to efficiently inhibit S-type amylase and this is another reason why macroamylse should be measured prior to isoenzyme measurement.

Based on the clinical presentation, routine investigations and isoenzyme results, tumor markers may be considered such as CA 125 or CA 19.9 bearing in mind their limitations.

The majority of ovarian cancers are diagnosed in women over 45 years old, with incidence rates higher in postmenopausal women and highest in women in the 60 to 64 year-old age group [63]. CA125 is somewhat more reliable in these older age groups, with raised serum CA125 in younger women less likely to be related to a diagnosis of ovarian cancer [63]. However, CA125 is not raised in up to 30% of women with ovarian cancer, especially those with potentially curable early-stage disease and so a CA125 result within the reference interval should never be used to exclude ovarian cancer [64, 65]. Several studies have explored the utility of CA 19-9 serum levels as a screening tool for pancreatic cancer in asymptomatic individuals as well as in patients with symptoms suspicious for pancreatic cancer [66, 67, 68].

As evident from these studies, given the suboptimal sensitivity and poor predictive value of CA 19-9 serum levels and low prevalence of pancreatic cancer in the general population, routine serum CA 19-9 level testing has no utility as a screening tool in asymptomatic patients.

Even among patients with symptoms suspicious for pancreatic cancer, elevated CA 19-9 serum levels is a poor predictor of pancreatic cancer with a predictive value of 0.5-0.9% [69].

CA19-9 can be raised in other malignant (gastric, cholangiocarcinomas) or benign conditions (acute and chronic pancreatitis, hepatocellular jaundice, cirrhosis, acute cholangitis or cystic fibrosis) further undermining the applicability of serum CA 19-9 as a screeening tool [65].

Among patients who present with a pancreatic mass, elevated CA 19-9 serum levels yield a much higher predictive value for diagnosing pancreatic cancer. Overall, an elevated serum CA 19-9 level has a sensitivity of 79-81% and a specificity of 82-90% for diagnosing pancreatic cancer in symptomatic patients [70].

Serum protein electrophoresis (SPEP) is indicated in suspected myeloma.

Since pancreatic hyperamylasemia can be associated with celiac disease (also associated with macroamylasemia as noted above) and viral hepatitis, tTG antibody and hepatitis screen can be useful in this setting.

Imaging Testing In a Proposed Diagnostic Algorithm

In cases of chronic hyperamylasemia where it is difficult to find a cause it is sometimes necessary to assess several organs. There are no published guidelines on selecting the imaging modality. In cases of unknown primary tumours, the initial standard evaluation is contrast enhanced CT of the chest, abdomen, and pelvis. This is essential to search for the primary tumor, evaluate the extent of disease and possible pattern of spread, and select amenable biopsy sites [71, 72].

FDG PET-CT whole body imaging is both a noninvasive and a very sensitive tomographic whole-body imaging modality, allowing for the detection of a primary tumor and complete tumor staging in single examination. It is another modality that has become more available and certainly would have a role in more occult lesions [73].

The radiation dose of a CT TAP would be concerning in a young patient. It would therefore be prudent to start the investigations with a chest Xray and an ultrasound of the pelvis to assess the lungs and ovaries. If the patient was having pancreatic imaging, then depending on the modality the chest and pelvis could also be assessed. Overall the main concerns are radiation dose and the age of the patient, one has always to consider and adhere to the ALARA principle (As Low As Reasonably Achievable.) when it comes to ionizing radiation.

In up to 75% of the cases, the tumor is located within pancreatic head mostly sparing the uncinate process [74]. Tumors in the pancreatic head often present early with biliary obstruction. Tumors in the body and tail can remain asymptomatic till late in disease stage [74]. Some patients can have multiphase CT initially and then serial CT studies to follow up any abnormalities detected. CT has a reported sensitivity between 76%-92% for diagnosing pancreatic cancer [75, 76, 77, 78, 79]. Brennan et al. assert that CT has an accuracy of 85%-95% for tumor detection, a positive predictive value of 89%-100% for unresectability and a negative predictive value of 45%-79% for resectability [80].

Nevertheless, multiphase CT exposes patient to a high radiation dose. Recently, the split-bolus CT protocol has been proposed for the detection and staging of pancreatic cancer [81]. Split-bolus multi detector CT technique, combining arterial phase (AP) and portal venous phase, allows an optimal pancreatic enhancement to detect normal pancreatic parenchyma and to maximize the difference in attenuation between the tumor and the background pancreatic parenchyma with a better tumor conspicuity, provides optimal synchronous arterial and mesenteric venous opacification evaluating potential tumor resecability, and reduces radiation dose [81]. In addition, split-bolus allows lymph nodes assessment, detection and characterization of the focal liver lesions [81].

Ultrasound has no ionizing radiation and also does not require contrast. It is however operator dependent and is also depended on body habitus. The real world accuracy

of conventional US for diagnosing pancreatic tumors is 50 to 70% [82]. Endoscopic US (EUS) provides ultra-high resolution images and is commonly accepted as the most sensitive technique for detection of small pancreatic head tumors [75, 83].

There are several imaging modalities each with positive and negative aspects. If there were no financial constraints and there was ease of access to MRI then this would represent an excellent first line modality. This would be particularly true in younger patients to limit the amount of radiation exposure. MRI can be used in imaging for pancreatic cancer in patients with equivocal findings at ultrasound or MDCT. MRI is commonly used to detect pancreatic cancer when a mass lesion is not identifiable on CT scan. There is however no significant diagnostic advantage of MRI over contrast- enhanced CT (sensitivity of 86% on CT *vs.* 84% on MRI) [84].

The choice of MRI or CT usually depends upon available local expertise and the clinician's comfort with one or the other radio-imaging technique. MRI, including morphologic and functional sequences, has become widely used in the diagnosis of pancreatic pathologies because of its very high soft-tissue contrast resolution, with an accuracy in the detection and staging of adenocarcinoma of 90-100% [85]. Administration of secretin during MRCP enhances the ductal morphologic features and increases the sensitivity of the diagnosis of chronic pancreatitis, compared with MRCP performed without secretin [86, 87].

LIMITATIONS

This article has limitations. The definition of chronic hyperamylasemia is arbitrarily defined. Because of the sparsity of the data, case series and case reports were included in the review of non-pancreatic hyperamylasemia, especially to demonstrate its varied etiology. The diagnostic algorithm, although based on the best available information is also based on expert opinion of the reviewers.

Conclusion

Chronic asymptomatic hyperamylasemia based on ethnic appropriate reference range can be further classified into nonpancreatic hyperamylasemia and pancreatic hyperamylasemia that is usually associated with elevated lipase activity.

In pancreatic hyperamylasemia, clinical evaluation, routine blood tests including liver, renal function tests, plasma lipids, glucose and calcium; abdominal ultrasonography and computed tomography are usually sufficient to exclude pancreatic diseases. Magnetic resonance imaging with secretin is useful to examine the Wirsung duct, exclude the presence of small intraductal tumors or pancreas divisum.

In case of non-pancreatic hyperamylasemia, the presence of macroamylase should be excluded first. Macroamylasemia is characterized by consistently increased amylase activity in the presence of normal lipase and low ACCR. The finding can occasionally be associated with some autoimmune conditions.

Salivary hyperamylasemia is typically seen with damage to the salivary glands. Alcohol abuse and anorexia nervosa should be considered in subjects without clinical evidence of parotitis. Tumors can also lead to ectopic production of amylase, usually of salivary type.

Chronic hyperamylasemia is hence a diagnostic challenge in clinical practice. Clinical-biochemical diagnostic algorithm for chronic persistent hyperamylasemia based on current best evidence is demonstrated in **Figure 2**.

Conflict of Interest

The authors declare that there is no conflict of interests.

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