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Fluctuating Amylase in a Female Child with Epilepsy and Global Developmental Delay and Absence of Pancreatitis

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Abstract

Amylase is an enzyme produced by both the pancreas and salivary glands to digest carbohydrates. The enzyme is used as a marker for acute pancreatitis however amylase may also be raised in salivary gland disease and other intra-abdominal conditions. We report a case of raised and fluctuating amylase concentrations in the absence of pancreatic or salivary gland disease. Whilst amylase levels fluctuated, serum lipase remained in the normal range and radiological investigation showed no evidence of pancreatitis.

Keywords

Amylase; Epilepsy; Pancreatitis; Saliva

Introduction

Amylase and lipase are pancreatic enzymes used as markers of acute pancreatitis due to their release from pancreatic acinar cells [1]. Patients with acute pancreatitis tend to present with severe abdominal pain, nausea and vomiting [1]. In acute pancreatitis, amylase tends to rise quickly reaching levels three times the upper limit of normal within 12 hours of presentation, returning to normal 3 to 5 days after resolution [1]. Amylase is also produced by the salivary glands (S-amylase), with salivary and pancreatic isoforms sharing 97% homology [2]. S-amylase is also found in the fallopian tubes, ovarian tissues, lungs, and prostate however these contributions to total salivary amylase are small [3]. Amylase in the saliva aids the breakdown of carbohydrates during mastication but also provides mucosal immunity [2]. Amylase may remain normal in individuals symptomatic of acute pancreatitis and may be raised in salivary gland disease and intra-abdominal inflammation [1]. We herein report a case of fluctuating amylase concentration in a patient with no evidence of pancreatitis or salivary gland disease.

Case Report

A 6-year-old girl with global developmental delay and drug-resistant multifocal epilepsy presented to the Emergency Department with increased frequency of seizures and behaviour indicating abdominal discomfort. She had presented with 4 seizures within 24 hours with no post-ictal periods (recovery period after a seizure). Biochemistry showed a raised amylase; 261 IU/L (reference range: 30-110 IU/L). Her prescribed anti-epileptic medications (Levetiracetam, Clobazam, Topiramate, and Buccolam) were stopped due to their association with pancreatitis and she was started on phenobarbitone. Cross sectional imaging showed no signs of pancreatitis. During her admission, amylase levels fluctuated from 34-5644 IU/L (Figure 1) with no evidence of continued abdominal discomfort or pancreatitis and no correlation to clinical interventions such as keeping nil by mouth. Serum lipase remained within the reference range (<67 U/L) during this admission. There was no evidence of hypertriglyceridaemia and no history or clinical evidence of salivary gland inflammation (Figure 1).

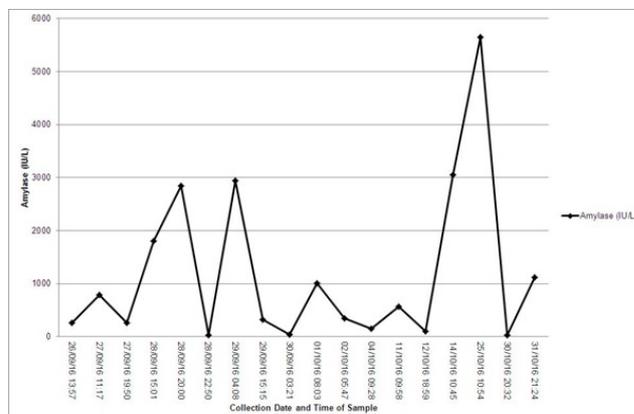


Figure 1 Concentration of amylase in serum samples taken from the patient during their admission.

The patient is known to have lissencephaly, a condition where brain gyri do not develop, caused by defective neuronal migration. She has associated microcephaly, global developmental delay and is not able to verbally communicate. She also has a percutaneous endoscopic gastrostomy (PEG) tube for feeding due to unsafe swallowing and reduced tolerance to oral feeding. The patient had a history of necrotizing pancreatitis of the body and tail of the pancreas of unclear aetiology 2 years prior to this admission.

A computed tomography (CT) scan showed the rectum and sigmoid to be distended with faeces, providing a possible explanation for the abdominal symptoms. All samples from the patient were correctly labeled, ruling out pre-analytical error. In order to further investigate, 2 samples with high amylase concentrations (taken on 14/10/2016 and 25/10/2016) were sent to 2 referral laboratories for amylase isoenzyme measurement. There was concern from her treating physicians about the unexplained fluctuation in amylase being due to an undiagnosed underlying pathology.

Discussion

The results of the isoenzyme measurement revealed that the majority of amylase in the samples was in the salivary isoform (S-amylase) (**Figure 2**). The isoenzyme electrophoresis ruled out macro amylase as a cause of the high amylase concentration.

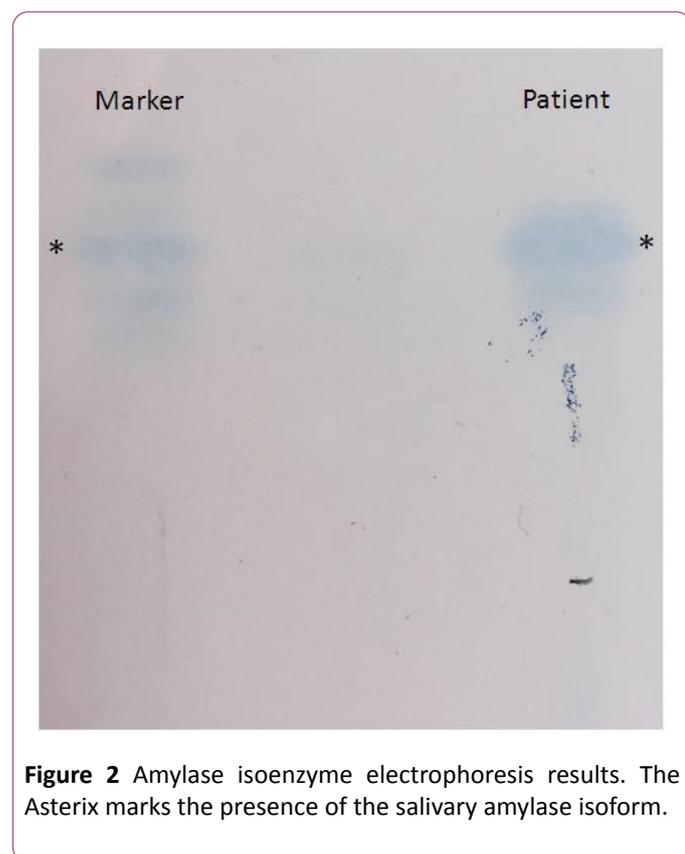


Figure 2 Amylase isoenzyme electrophoresis results. The Asterix marks the presence of the salivary amylase isoform.

Salivary amylase is synthesized and secreted from acinar cells in the salivary glands and has a half-life of approximately 10 minutes and is rapidly cleared [4,5]. Salivary amylase concentrations are variable between individuals and this

variation may be due to environmental factors, such as stress or genetic factors.6 Individuals may have copy number variations (CNVs) in the amylase gene, *AMY1*, with a range of 2 to 15 diploid copies reported [6]. Mandel et al. found a positive correlation between the number of CNVs present and salivary amylase concentration when studying saliva with a range of salivary amylase levels from 1.31 U/mL to 371 U/mL [6]. It has been suggested that the differences in CNVs observed may originate from historical population differences in starch intake; populations that consumed a high-starch diet would present with more *AMY1* gene copies.6 Additionally, there are three known single nucleotide polymorphisms (SNPs) in the *AMY1* gene; *AMY1A*, *AMY1B*, and *AMY1C*, which may also contribute to differences in amylase expression [6]. Diurnal variation can also affect salivary amylase concentration with levels peaking at 156.87 U/mL in the late afternoon [7]. None of the evidence presented above would explain the wide fluctuation in amylase levels seen in this patient.

Acinar cells synthesise the fluid component of saliva as well as amylase and both components are released together [2]. Therefore, any factor affecting the saliva flow rate may equally affect salivary amylase concentration [2]. On further review of the patient's history, it was noted that the parents had reported that she drools constantly and this increase in salivation may explain the raised salivary amylase concentration. The patient received a botulinum toxin A injection to the submandibular glands in 2015 and uses hyoscine hydrobromide patches to control salivation. Botulinum toxin is used as a therapy for excess salivation as the toxin inhibits the action of cholinergic receptors in the salivary glands to reduce saliva flow rate however, adrenergic innervation is not affected and subsequently protein concentration does not change [8]. The effect of the toxin on the salivary glands is only temporary, with therapy lasting anywhere from 1.5 to 6 months [9]. Therapy must be repeated for permanent drooling states [8].

Acinar cells are innervated with both sympathetic and parasympathetic nerve fibres, which control the basal release of salivary amylase; activation of sympathetic salivary gland innervations may lead to an increase in salivary amylase [4] Observations have highlighted that amylase concentration in the saliva increases after exercise [2] with a positive correlation between salivary amylase and norepinephrine with levels rising to 600 U/mL [5]. In support of this association, the application of beta-adrenergic receptor blockers reduced the increase in amylase during a stress response and administration of an alpha-2 adrenergic receptor agonist increased salivary amylase [10] Stimulation of the sympathetic innervations due to stress may subsequently inhibit parasympathetic innervation stimulation. The parasympathetic innervations stimulate saliva flow rate, therefore inhibition would result in decreased saliva flow with an unchanged protein contribution. This would also lead to a high amylase concentration separate to an increase in secretion [10].

In epilepsy, all autonomic function is altered during ictal, post-ictal and inter-ictal stages including, sympathetic, parasympathetic and adrenal medullary systems [11]. Complex

seizure states often result in sympathetic activation, however, parasympathetic activity may predominate in some individuals, leading to an increase in salivation [11] Patients with epilepsy report that seizures are triggered or exacerbated by fluctuations in emotion, mental and physiological states such as tiredness and sleep deprivation and that these disturbances are related to exaggerated autonomic activation [12].

Conclusion

The explanation for the patient's raised salivary amylase concentration is most likely that the increased frequency of seizures contributed to activation of the sympathetic nervous system and subsequently an increase in salivary amylase via the sympathetic innervations of the salivary gland [4]. The fluctuation in amylase may be due to the short half-life of the salivary isoform, 5 or the depletion of secretory granules where salivary amylase is stored [4]. This was conveyed to her treating clinician and both the medical team and the patient's relatives were reassured. The patient no longer requires amylase monitoring, however if there is clinical suspicion of pancreatitis, lipase measurement is recommended.

In the literature there has been one case reported of increased amylase after seizures, however, there are currently no reports of fluctuation in salivary amylase concentration in epileptic patients and to the best of our knowledge this is the first such case report.

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Declaration of Conflicting Interests

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