Macrolipasemia variant of macroenzymes: An endocrine laboma

LOKESH KUMAR SHARMA, RASHMI RASHI DATTA, ANSHITA AGGARWAL, NEERA SHARMA, DEEP DUTTA

ABSTRACT

Macroenzymes, formed by polymerization of physiological enzymes with immunoglobulins, have slower renal clearance rates due to their higher molecular mass. They are usually incidentally detected, have no pathophysiological importance, and can potentially lead to over-treatment and iatrogenic morbidity. We present, possibly for the first time, a macrolipasemia variant of macroenzyme, detected in a 14-year-old girl with type-1 diabetes admitted with severe hyperglycaemia and pain abdomen. Raised lipase levels (414 U/L), initially raised the suspicion of underlying pancreatitis, which was ruled out by the clinical symptoms and normal ultrasound and CT imaging of the pancreas. Upper gastrointestinal endoscopy revealed pangastritis, which could explain the mild upper abdominal pain in the child. She improved with proton pump inhibitor therapy and was discharged after 5 days of hospital admission after good glycaemic control using multiple subcutaneous injections of insulin. Post-polyethylene glycol (PEG) precipitation, the recovery of lipase activity in PEG treated serum sample was 30.6% (127 U/L), which confirmed the presence of macrolipase. An increased clinical suspicion and performing a cheap reliable test (PEG precipitation), whenever there is clinical biochemical discordance can help us in diagnosing more patients with macroenzymes and macrolipasemia.

Natl Med J India 2024;37:28–9

INTRODUCTION

Macroenzymes are normal serum enzymes that form high molecular mass complexes by polymerization, or by linking with other serum components having high molecular mass, mostly immunoglobulins.[1,2] They have a slower clearance rate owing to their high molecular mass, thus accumulating in serum and enhancing the respective enzyme activity. These enzyme forms are usually detected when patients have continuously elevated serum enzyme activity that cannot be explained and is inconsistent with the general clinical picture. Macroenzymes are true 'labomas', viz. incidental biochemical abnormality of no underlying clinical significance.[3,4] Failure to detect macroenzymes can lead to unnecessary over-treatment, exposing the patient to increased risks of iatrogenic morbidity. We present, possibly for the first time, an incidentally detected macrolipasemia in a child admitted with uncontrolled type-1 diabetes (T1D).

Atal Behari Vajpayee Institute of Medical Sciences (ABVIMS) and Dr Ram Manohar Lohia (RML) Hospital, New Delhi 110001, India
LOKESH KUMAR SHARMA, RASHMI RASHI DATTA, NEERA SHARMA Department of Biochemistry
ANSHITA AGGARWAL Department of Endocrinology

Center for Endocrinology, Diabetes, Arthritis and Rheumatism, Dwarka, New Delhi 110075, India
DEEP DUTTA Department of Endocrinology

Correspondence to DEEP DUTTA; *deepdutta2000@yahoo.com*

[**To cite:** Sharma LK, Datta RR, Aggarwal A, Sharma N, Dutta D. Macrolipasemia variant of macroenzymes: An endocrine laboma. *Natl Med J India* 2024;**37:**28–9. DOI: 10.25259/NMJI_161_21]

THE CASE

A 14-year-old girl with T1D of 3 years duration was admitted to the Department of Endocrinology with mild pain abdomen, uncontrolled diabetes and glycaemic variability. Initial investigations of normal pH on blood gas analysis, absence of ketones in urine and blood ruled out diabetic ketoacidosis. Investigations to rule out any underlying occult infections (urine analysis, blood culture, chest X-ray) as the cause for the sudden worsening of glycaemic control in the past few weeks were normal. Biochemical investigations showed raised serum lipase (414 U/L; normal <300 U/L) with normal amylase (61 U/L; normal <110 U/L), raising the suspicion of underlying pancreatitis (Table I). Serum lipase continued to be high (387 U/L) even after euglycaemia with optimal insulin therapy. However, the child did not have typical clinical features associated with pancreatitis (severe pain radiating to the back, nausea, vomiting, anorexia, altered bowel habits). Systemic examination was normal (soft abdomen with normal bowel sounds, normal cardiac and respiratory examination). Ultrasound of the upper abdomen did not reveal any pancreatic abnormality. Computed tomography (CT) of the upper abdomen also revealed normal pancreas and adjacent structures. Biochemical tests related to autoimmunity involving the liver and pancreas were negative (antimitochondrial antibody, anti-liver kidney microsomal [LKM] antibody, SP100 nuclear antigen, soluble liver antigen [SLA] test). Certain infections that are associated with falsely raised lipase levels were also ruled out using biochemical tests (HIV, hepatitis C, hepatitis B and typhoid). Upper gastrointestinal endoscopy revealed pangastritis, which could explain the mild upper abdominal pain. The patient improved with oral proton pump inhibitor therapy.

In view of clinical and biochemical discordance with regard to raised lipase levels, macrolipase was considered as a possible cause of elevated enzyme levels. Hence, urinary lipase was done, which was normal. Polyethylene glycol (PEG) precipitation was done to check for the presence of macrolipase. For the PEG precipitation test, 25% of PEG solution was prepared by dissolving 6.25 g of PEG in 15 ml of freshly prepared phosphate buffered saline (pH 7.4). The mixture was left at

TABLE I. Biochemical profile of the patient

Parameter	Units	Result	Normal range
Sodium	mmol/L	139	130–150
Potassium	mmol/L	4.7	3.5–5.5
Urea	mg/dl	48	15–45
Creatinine	mg/dl	0.4	0.6–1.2
Total bilirubin	mg/dl	0.5	0.2–1.2
Aspartate aminotransferase	U/L	43	15–50
Alanine aminotransferase	U/L	40	15–50
Alkaline phosphatase	U/L	245	50–130
Total protein	g/dl	7.9	6.0–8.0
Albumin	g/dl	4.4	3.5–5.5
Amylase	U/L	61	30–110
Lipase	U/L	414	23–300

4–8 °C for 24 hours. Phosphate buffered saline was added further to make the volume up to 25 ml. The solution is stable to be used for 3 months at a temperature of 4–8 °C. Similar quantities of PEG solution and patient serum sample (200 µl) were mixed in an aliquot and held at room temperature for 10 minutes before centrifugation. Equal volume of patient serum sample was mixed with distilled water to be used as control for comparison. Both the samples were then subjected to cold centrifugation at 4 °C per 3000 rpm for 30 minutes. Lipase activity was estimated on both the supernatants of the PEG diluted and distilled water diluted sample. Percentage recovery was determined by dividing the value obtained on the supernatant by the pretreatment value. Considerable variation was observed in the pretreatment lipase levels and the results obtained from the supernatants of distilled water diluted and PEG diluted samples (127 U/L). The recovery of lipase activity in PEG treated serum sample was 30.6%, which is significant for presence of macrolipase. The values obtained from the PEG treated sample was within the normal biological reference range (20–300 U/L). Hence, the unexplained elevation of lipase activity in the patient was attributed to macrolipase in the blood. The patient was discharged after 5 days of admission after ensuring a good glycaemic control with multiple injections of subcutaneous insulin.

DISCUSSION

Elevated pancreatic enzymes are not common in hyperglycaemia without ketosis. In fact, with a longer duration of both type 1 and type 2 diabetes, a progressive decline in circulating pancreatic enzymes have been documented.[5] Pancreatic enzymes may be increased in people living with diabetes because of various reasons. Use of incretin-based therapies (both glucagon-like peptide-1 receptor agonists [GLP1Ra] and dipeptidyl peptidase-4 [DPP4 inhibitors]) is perhaps the most common cause of elevated pancreatic enzymes in type 2 diabetes.[6] Use of incretin-based therapies have been linked with increased occurrence of pancreatitis.[7] Diabetic ketoacidosis is known to be associated with reversible elevation of pancreatic enzymes, which gets corrected with restoration of euglycaemia and needs no specific treatment. Diabetes *per se* is a risk factor of pancreatitis, which is associated with raised pancreatic enzymes. Certain forms of diabetes such as fibrocalculous pancreatic diabetes are associated with disproportionately higher risks of raised pancreatic enzymes and pancreatitis.[8]

Measurement of different enzymes in the blood is often done to rule out different disease states. Increased enzyme levels in blood may rarely be due to the presence of macroenzymes. They do not reflect any disease states and are often incidentally detected labomas. However, their presence interferes with the interpretation of laboratory reports and may lead to diagnostic and therapeutic errors and misadventure.[1] The likelihood of the presence of macroenzymes should be suspected whenever there is a discordance between the biochemical results and the clinical profile of the patient. The commonly reported macroenzyme in the literature is macroenzyme aspartate aminotransferase (macro-AST).[9] Macrolipase has never been reported to the best of our knowledge.

In our case, isolated elevation of lipase activity was detected, which was discordant with the patient's clinical picture. A broad array of diagnostic tests were performed, which did not reveal any noteworthy findings that could be attributed to raised enzyme levels. A PEG precipitation test was then done and macrolipase was detected despite normal lipase level in the patient. PEG precipitation test has a simple technique that acts by precipitating the immunoglobulins and thereby removing the enzymes complexed to them. This enables the detection of true enzyme activity. For the concerned patient, true enzyme activity was reported to be within the normal biological reference range, which did not warrant any therapeutic intervention.

Identification of macroenzymes is clinically important and should be a vital part of diagnostic work-up, to preclude the use of unnecessary expensive and invasive diagnostic procedures.[10,11] Macroenzymes persist in the blood for a long time hence the finding should be clearly documented in the patient's medical records to avoid future misinterpretation of the patient's serum enzyme levels.[12–14] The patient should be informed and reassured that the occurrence of this form of enzyme requires no specific therapeutic intervention.

We highlight the existence of macrolipasemia as a variant of macroenzymes, which has been reported possibly for the first time. An increased clinical suspicion and doing PEG precipitation, whenever there is clinical biochemical discordance can help us in diagnosing more patients with macroenzymes and macrolipasemia.

Conflicts of interest. None declared

REFERENCES

1 Remaley AT, Wilding P. Macroenzymes: Biochemical characterisation, clinical significance, and laboratory detection. *Clin Chem* 1989;**35:**2261–70.
2 Sturk A, Sanders GT. Macro enzymes: Prevalence, composition and clinical relevance. *J Clin Chem Clin Biochem* 1990;**28:**65–81.
3 Chittawar S, Dutta D, Khandelwal D, Singla R. Neonatal endocrine labomas—Pitfalls and challenges in reporting neonatal hormonal reports. *Indian Pediatr* 2017;**54:**757–62.
4 Dutta D, Chowdhury S. Endocrine labomas. *Indian J Endocrinol Metab* 2012;**16** (Suppl 2):S275–S278.
5 Aughsteen AA, Abu-Umair MS, Mahmoud SA. Biochemical analysis of serum pancreatic amylase and lipase enzymes in patients with type 1 and type 2 diabetes mellitus. *Saudi Med J* 2005;**26:**73–7.
6 Sayiner ZA, Inan Demiroðlu G, Akarsu E, Araz M. The relationship between dipeptidyl peptidase-4 inhibitor usage and asymptomatic amylase lipase increment in type 2 diabetes mellitus patients. *Turk J Pharm Sci* 2020;**17:**68–73.
7 Singh AK, Gangopadhyay KK, Singh R. Risk of acute pancreatitis with incretin-based therapy: A systematic review and updated meta-analysis of cardiovascular outcomes trials. *Expert Rev Clin Pharmacol* 2020;**13:**461–8.
8 Anne B, Ghosh S, Ghosh I, Ray S, Chowdhury S, Dutta D. Prevalence of end-organ damage, beta cell reserve, and exocrine pancreas defect in fibrocalculous pancreatic diabetes: An eastern India perspective. *Indian J Endocrinol Metab* 2019;**23:** 438–45.
9 Rubin AS, Sass DA, Stickle DF. Distribution of serum concentrations reported for macroenzyme aspartate aminotransferase (macro-AST). *Pract Lab Med* 2017;**8:** 65–9.
10 Mifflin TE, Bruns DE. University of Virginia case conference. Macroamylase, macro creatine kinase, and other macroenzymes. *Clin Chem* 1985;**31:**1743–8.
11 Galasso PJ, Litin SC, O'Brien JF. The macroenzymes: A clinical review. *Mayo Clin Proc* 1993;**68:**349–54.
12 Wilding P, Cooke WT, Nicholson GI. Globulin-bound amylase: A cause of persistently elevated levels in serum. *Ann Intern Med* 1964;**60:**1053–9.
13 Peace MA. The CK and LD macroenzymes. *Lab Manage Today* 1984:29-41.
14 Klonoff DC. Macroamylasemia and other immunoglobulin-complexed enzyme disorders. *West J Med* 1980;**133:**392–407.