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Case Report

New-Onset Type 1 Diabetes in a Child With Diabetic Ketoacidosis and Severe Hypertriglyceridemia Without Pancreatitis

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Abstract

Hypertriglyceridemia is a complication of diabetic ketoacidosis (DKA) secondary to insulin deficiency inhibiting lipoprotein lipase and increasing lipolysis, but it is rare in children. A 7-year-old boy with history of autism spectrum disorder (ASD) presented with abdominal pain, vomiting, and "heavy breathing." Initial laboratory tests revealed pH 6.87 and glucose 385 mg/dL (21.4 mmol/L), consistent with new-onset diabetes and DKA. His blood appeared lipemic; triglycerides were 17 675 mg/dL (199.6 mmol/L) with normal lipase (10 units/L). He received intravenous insulin and DKA resolved within 24 hours. Insulin infusion continued through day 6 for management of hypertriglyceridemia; triglycerides decreased to 1290 mg/dL (14.6 mmol/L) during this period. He never developed pancreatitis (lipase peaked at 68 units/L) or required plasmapheresis. With his ASD history, he had a restrictive diet high in saturated fat, which included up to 30 breakfast sausages daily. His triglycerides normalized after discharge. Severe hypertriglyceridemia can complicate DKA in newly diagnosed type 1 diabetes (T1D). Hypertriglyceridemia can be safely managed with insulin infusion in the absence of end-organ dysfunction. This complication should be considered in patients with DKA at diagnosis of T1D.

Key Words: hypertriglyceridemia, diabetic ketoacidosis (DKA), type 1 diabetes

Abbreviations: A1c, glycated hemoglobin; ASD, autism spectrum disorder; DKA, diabetic ketoacidosis; HSL, hormone-sensitive lipase; LPL, lipoprotein lipase; T1D, type 1 diabetes; VLDL, very low-density lipoprotein.

Introduction

Hypertriglyceridemia is a known complication of diabetic ketoacidosis (DKA). Insulin deficiency leads to inhibition of lipoprotein lipase (LPL), which causes decreased removal of very low-density lipoprotein (VLDL) particles from the circulation and decreased hydrolysis of triglycerides from chylomicrons [1]. The net effect is to increase the concentration of VLDL and chylomicrons in the blood, both of which have high triglyceride content. Additionally, insulin deficiency causes decreased inhibition of hormone-sensitive lipase (HSL), which can increase lipolysis, leading to increased circulating free fatty acids. Up to 8% of adults presenting with DKA have concurrent severe hypertriglyceridemia, but it is rare in children [2]. Elevated triglycerides can be missed if not clinically apparent as lipids are rarely measured as part of the DKA evaluation. This case report expands on the clinical association of hypertriglyceridemia with DKA in a 7-year-old boy with a pertinent comorbidity and unusual dietary history.

Case Presentation and Diagnostic Assessment

A 7-year-old boy with past medical history of autism spectrum disorder (ASD) presented to an outside hospital with 1 day of abdominal pain and vomiting with "heavy breathing." His parents reported weight loss, anorexia, and polyuria/polydipsia, with secondary nocturnal enuresis that had progressed over the 5 months prior to presentation. He had venous pH 6.87, bicarbonate 4.8 mmol/L, and glucose 385 mg/dL (21.4 mmol/L), consistent with new-onset diabetes in severe DKA. Abdominal ultrasound, obtained due to severe abdominal pain, showed small bowel-small bowel intussusception with no mention of visualization of the pancreas. A regular insulin infusion was initiated at 0.1 units/kg/h and he was transferred to our institution. While in transit, laboratory samples were drawn and blood appeared lipemic, prompting triglyceride measurement, which was elevated at 17 675 mg/dL (199.6 mmol/L). His lipase was normal at 10 units/L and amylase was low at 20 units/L. His pH had improved to 7.03 on arrival, beta-hydroxybutyric acid was elevated at 8.0 mmol/L, and glycated hemoglobin (A1c) was elevated at 9.9%. Type 1 diabetes (T1D)-associated autoantibodies were assayed during the hospitalization (positive results returned after discharge). These and other pertinent laboratory tests on admission can be found in Table 1.

His past medical history was relevant for ASD. His diet prior to presentation was very restrictive, as he ate mostly high-

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Table 1. Laboratory values on presentation to the hospital

LAB	VALUE	REFERENCE RANGE
Venous pH	**7.03**	7.31-7.41
Bicarbonate	**3 mmol/L**	22-30 mmol/L
Potassium	**6.2 mmol/L**	3.2-4.5 mmol/L
Glucose	**274 mg/dL (15.2 mmol/L)**	61-199 mg/dL (3.4-11.0 mmol/L)
Beta-hydroxybutyric acid	**8.90 mmol/L**	≤0.29 mmol/L
Sodium	143 mmol/L	135-148 mmol/L
Creatinine	0.42 mg/dL (37.1 µmol/L)	0.3-0.7 mg/dL (26.5-61.9 µmol/L)
Amylase	**20 unit/L**	40-220 unit/L
Lipase	10 unit/L	7-60 unit/L
A1c	**9.9%**	4.0%-6.0%
Direct LDL	8 mg/dL (0.2 mmol/L)	0-109 mg/dL (0-2.8 mmol/L)
HDL	**16.5 mg/dL (0.4 mmol/L)**	>45 mg/dL (>1.7 mmol/L)
Triglycerides	**17 675 mg/dL (199.6 mmol/L)**	0-100 mg/dL (0-1.1 mmol/L)
GAD65 antibody	**31.0 IU/mL**	0.0-5.0 IU/mL
Insulin antibody	<0.4 unit/mL	0.0-0.4 unit/mL
IA-2 antibody	<5.4 unit/mL	0.0-7.4 unit/mL
Zinc transporter 8 antibody	**>500 unit/mL**	0.0-15.0 unit/mL

Abbreviations: A1c, glycated hemoglobin; GAD65, glutamic acid decarboxylase (65 kDa); HDL, high-density lipoprotein; IA-2, islet cell antigen 2; LDL, low-density lipoprotein.

fat foods secondary to his dietary preferences compounded by ASD. On some days he ate up to 30 breakfast sausages. Family history was notable for celiac disease in his mother and T1D and thyroid disease in his maternal grandmother. There was no known family history of lipid disorders, and no previous lipid panel was available for the patient.

On physical exam, he was tachycardic with heart rate 164 beats per minute, blood pressure 123/76 mmHg, and oxygen saturation 96%. Height was 122.5 cm (23rd percentile) and weight was 24 kg (38th percentile), down from 32 kg at a pediatrician's visit 5 months prior. His body mass index was 21.1 (57th percentile). He had normal subcutaneous fat distribution and no xanthomas or acanthosis nigricans were noted.

Treatment

Insulin infusion at 0.1 units/kg/h was unable to improve acidosis with pH remaining 7.24 to 7.26 from hours 7 to 18 of infusion, so the rate was increased to 0.125 units/kg/h with subsequent normalization of pH (Fig. 1). Lipemia can impact accuracy of many serum chemistries; however, our laboratory standard includes ultracentrifugation prior to processing with severe hypertriglyceridemia, as in this case. Blood gas analysis is not impacted by elevated triglyceride levels [3].

Given his significant weight loss and dehydrated state, it was thought that his true hydrated weight was higher, leading to higher insulin requirements. Additionally, the hypertriglyceridemia itself likely contributed to insulin resistance and provided a high concentration of substrate for ketone formation. Repeat ultrasound confirmed ileo-ileal intussusception, which self-resolved, as did his abdominal pain. The pancreas was not visualized on the ultrasound. His acidosis resolved within 24 hours, but his status remained nothing-by-mouth and the insulin infusion was continued to manage hypertriglyceridemia. Dextrose-containing fluids (12.5%) with 40 mEq potassium/liter were infused at twice the maintenance rate to maintain his blood glucose levels. Lipase remained within the normal range throughout this period, only rising above the upper limit of normal once on hospital day 5 (68 unit/L). Plasmapheresis was considered but was not pursued given no pancreatitis or other end-organ dysfunction. The insulin infusion rate was decreased multiple times for relative hypoglycemia over the 6-day period (Fig. 1).

Given absence of pancreatitis and improved appetite on hospital day 5, he began enteral intake of a low-fat diet. With his limited dietary preferences, he ate very little while restricted to a low-fat diet in the hospital. Insulin infusion was discontinued on day 6, when triglycerides reduced to 1290 mg/dL (14.6 mmol/L). He was transitioned to a subcutaneous insulin regimen with multiple daily injections using carbohydrate ratio and correction factor. His diet was liberalized on day 7 with no increase in triglycerides or amylase/lipase. His preferred foods while hospitalized included chicken tenders, French fries, and ice cream.

Outcome and Follow-up

He was followed closely after discharge by both endocrinology and preventive cardiology teams. Tests for GAD65 and Zinc Transporter 8 autoantibodies returned positive results (Table 1), confirming the suspected diagnosis of autoimmune T1D. Within 2 weeks, his triglycerides had normalized but his total cholesterol and low-density lipoprotein (LDL) remained elevated (Table 2). His food preferences and ASD made dietary changes difficult. He has had ongoing visits with a dietitian, and his fruit and vegetable intake has increased, but his parents continue to report rigidity in food choices. His A1c has been above target in the 30 months since initial presentation (persistently >9%, most recently 9.4%) and continuous glucose monitoring time-in-range has been below target (persistently <25%, most recently 8%) despite reported adherence to his basal-bolus insulin regimen. Triglycerides have remained normal.

Discussion

Hypertriglyceridemia is a known but relatively uncommon complication of DKA that has been described in multiple pediatric case reports previously [2, 4, 5]. This case is unique in that this is one of the highest reported triglyceride levels in the pediatric literature and the absence of pancreatitis with this degree of hypertriglyceridemia is unusual [6]. Insulin deficiency inhibits LPL, which decreases VLDL and chylomicron clearance leading to elevated triglyceride levels [1, 7]. Insulin deficiency also causes increased HSL activity, leading to lipolysis and increased free fatty acids [7]. It is critical to identify severe hypertriglyceridemia in the setting of DKA given possibility of pancreatitis.

When hypertriglyceridemia causes pancreatitis, it must be treated alongside the DKA with more aggressive fluid resuscitation and prolonged nothing-by-mouth status. If pancreatitis

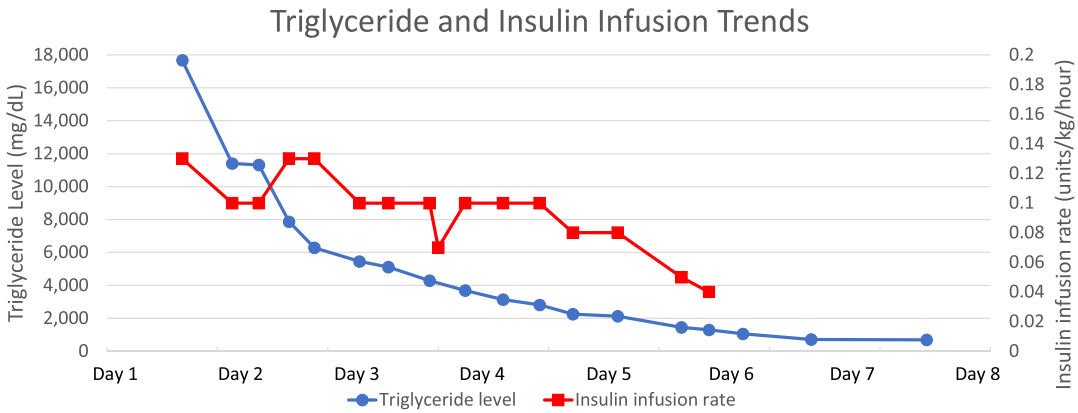

Figure 1. Triglyceride and insulin infusion trend. Triglyceride levels and insulin infusion rates throughout the hospitalization.

Table 2. Cholesterol trend after discharge

LAB	2 WEEKS AFTER DISCHARGE	6 MONTHS AFTER DISCHARGE	REFERENCE RANGE
Total cholesterol	**250 mg/dL (6.5 mmol/L)**	**240 mg/dL (6.2 mmol/L)**	<200 mg/dL (<5.2 mmol/L)
HDL	83 mg/dL (2.1 mmol/L)	77 mg/dL (2.0 mmol/L)	>45 mg/dL (>1.7 mmol/L)
LDL	**157 mg/dL (4.1 mmol/L)**	**145 mg/dL (3.8 mmol/L)**	0-109 mg/dL (0-2.8 mmol/L)
Triglycerides	75 mg/dL (0.8 mmol/L)	74 mg/dL (0.8 mmol/L)	0-100 mg/dL (0-1.1 mmol/L)

Abbreviations: HDL, high-density lipoprotein; LDL, low-density lipoprotein.

is not present, it is important to lower triglyceride levels rapidly to prevent its development. This patient did have abdominal pain on presentation, but this was found to be secondary to ileo-ileal intussusception and the pain resolved with resolution of the intussusception. While his lipase did once rise above the normal range (10-65 unit/L) to 68 unit/L, this was not associated with significant abdominal pain and thus he did not meet criteria for pancreatitis.

The mechanism of pancreatitis in hypertriglyceridemia has not been completely described, but recent progress has been made in understanding this pathophysiology. Lipase within pancreatic acinar cells breaks down triglycerides into free fatty acids, which causes ischemia and activates trypsin, leading to a cascade of pancreatic self-injury [8]. Increased fatty acid levels can promote inflammatory cascades, disturb pancreatic microcirculation, elevate cytosolic Ca^{2+} levels, and decrease antioxidant activity leading to increased oxidative stress [8]. With triglyceride levels this high, it is unusual that this patient did not develop pancreatitis; one cross-sectional study found that people with triglyceride levels >7750 mg/dL (87.5 mmol/L) had a 66.6% prevalence of acute pancreatitis [6], and this patient's presenting triglyceride level was more than double that value.

Management of hypertriglyceridemia in the acute setting can be achieved with heparin infusion, insulin infusion, hemofiltration, or plasmapheresis [9]. As this patient did not develop pancreatitis or other signs of end-organ dysfunction (such as lactic acidosis, multi-organ failure, or systemic inflammation), insulin infusion was chosen. Insulin activates LPL and inhibits HSL, restoring physiologic energy metabolism and lowering triglyceride levels [7]. After 6 days of therapy, with triglyceride level decreased to 1290 unit/L and improved appetite, the decision was made to discontinue insulin infusion. While some guidelines recommend continuing insulin infusion until triglycerides drop below 500 unit/L [9], the patient's overall clinical status had improved, with return of appetite, prompting discontinuation. His triglycerides continued to downtrend with subcutaneous insulin therapy for management of his T1D.

In addition to insulin deficiency, there are multiple potential contributors to the severity of this patient's hypertriglyceridemia. The parents reported 5 months of symptoms consistent with hyperglycemia prior to diagnosis, suggesting that the insulin deficiency may have been prolonged. He could have an underlying genetic cause of hyperlipidemia, although there was no reported family history of lipid disorders. His triglycerides have normalized without any targeted therapy, which suggests against familial hypertriglyceridemia. There has been a reported case of heterozygous *LPL* mutation causing hypertriglyceridemia in the setting of DKA, which normalized with subcutaneous insulin therapy [5]. Genetic testing has been considered for this patient but has not been performed.

The patient did have a restrictive diet high in saturated fat, likely compounded by his ASD. Limited diets are seen in a variety of people with T1D, from developmentally appropriate toddlers to people with sensory issues, like this patient. There are multiple diets which can contribute to hypertriglyceridemia, including those high in saturated fat, which may be seen in people eating low-carbohydrate or "keto" diets, and those high in sugar or refined carbohydrates, which are increasingly common in the developed world [10]. Notably, lipids are often intentionally not measured in the setting of DKA to avoid overdiagnosis of lipid disorders in the setting of transient insulin deficiency.

This case of hypertriglyceridemia in the setting of DKA and new-onset T1D highlights the importance of holistically

evaluating people with DKA. The patient's lipemic serum was the only indication of hypertriglyceridemia, and with the risk of pancreatitis it is important to normalize triglyceride levels rapidly. While an underlying genetic cause has not been ruled out in this patient, his dietary restrictions and likely prolonged insulin deficiency are also important contributing factors. A similar case was reported of a 10-year-old girl with triglyceride level of 16 334 mg/dL (184.6 mmol/L) in the setting of DKA who was not found to have an underlying lipid metabolism disorder [4]. Despite his severely elevated triglyceride level, which is the highest we found associated with DKA in the pediatric literature, he was able to be managed with insulin infusion and did not require plasmapheresis [2]. Clinicians should consider hypertriglyceridemia in patients presenting with DKA, especially those with risk factors such as family history or diet.

Learning Points

- Hypertriglyceridemia can complicate diabetic ketoacidosis but is rare in children.
- In the absence of end-organ dysfunction, even severe hypertriglyceridemia can be managed with insulin infusion rather than plasmapheresis.
- Providers should consider measuring triglycerides in the setting of DKA, particularly in individuals with risk factors for hypertriglyceridemia (such as family history or diet), given the potential impact on management.

Contributors

All authors made individual contributions to authorship. R.J.V. and L.M.B.L. were both involved in diagnosis and management of the patient and manuscript submission. R.J.V. was the lead on the original draft and both R.J.V. and L.M.B.L. contributed to review and editing. All authors reviewed and approved the final draft.

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Disclosures

None declared.

Informed Patient Consent for Publication

Signed informed consent obtained directly from the patient's relatives or guardians.

Data Availability Statement

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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