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CASE REPORT

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SEVERE HYPERTRIGLYCERIDEMIA IN THE COURSE OF KETOACIDOSIS IN A PATIENT WITH NEWLY DIAGNOSED TYPE 1 DIABETES MELLITUS

Eliza Skala-Zamorowska[1], Halla Kaminska[1, 5], Wladyslaw Gawel[2, 5], Lukasz Szarpak[3, 5], Wojciech Mlynarski[4], Przemyslawa Jarosz-Chobot[1]

[1]Deptartment of Children's Diabetology and Pediatrics, Medical University of Silesia, Katowice, Poland
[2]Department of Surgery, The Silesian Hospital in Opava, Opava, Czech Republic
[3]Maria Sklodowska-Curie Medical Academy, Warsaw, Poland
[4]Department of Paediatrics, Oncology, Haematology and Diabetology, Medical University of Lodz, Poland
[5]Polish Society of Disaster Medicine, Warsaw, Poland

ABSTRACT

BACKGROUND: One of the most serious complications in delayed diagnosis of DKA is hypertriglyceridemia (HTG), Prevalence of mild hypertriglyceridemia is found in about 50% of patients with diabetic ketoacidosis (DKA). Prevalence of severe hypertriglyceridemia [TG > 22.4 mmol/L (> 1959 mg/dL)] was found in about 1–8% of adults with DKA, but few data have been reported in children with severity ranging from asymptomatic to severe acute pancreatitis.

CASE PRESENTATION: A 2-year-old-girl with a 2 weeks history of generalized weakness, polydipsia, polyuria, and vulvar candidiasis was admitted to the Intensive Care Unit with clinical signs of DKA. Our patient was met the diagnostic criteria for DKA (pH 7.1, HCO^{3-} 8.8 mmol/L, BE -21.1 mmol/L), glucose level of > 22 mmol/L (556 mg/dl). Initial biochemical analysis showed hyperlipidemia [TG 11470 mg/dL (131.1 mmol/L)], amylase 28 U/L. Her blood demonstrated a grossly lipemic appearance and her lipemic condition disturbed the results of other biochemical blood investigations. The objective of this case report is to present and describe the clinical features, laboratory investigations, case management, and natural course of hypertriglyceridemia in a 2-year-old girl with DKA.

CONCLUSIONS: Lipemia secondary to severe HTG may exist in new-onset T1DM with DKA. Diabetic lipemia can be caused not only by profound insulin deficiency. An additional factor which should be taken into consideration in very young children is breastfeeding, which is associated with increased mean total cholesterol (TC) and LDL levels. Moreover, severe hypertriglyceridemia may result in mutations of genes encoding lipoprotein lipase (LPL).

KEY WORDS: type 1 diabetes mellitus; hypertriglyceridemia; diabetic ketoacidosis; total cholesterol; lipoprotein lipase

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ADDRESS FOR CORRESPONDENCE:
Halla Kaminska, Department of Children's Diabetology and Pediatrics School of Medicine in Katowice
Medical University of Silesia, 16 Medyków St, 40–752 Katowice, Poland
e-mail: halla.kaminska@gmail.com
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INTRODUCTION

Diabetic ketoacidosis (DKA) is an acute complication occurring mainly in the course of type 1 diabetes mellitus. This metabolic complication requires emergency treatment. Diagnostic criteria for DKA include hyperglycemia (BS > 200 mg/dL), ketosis, and metabolic acidosis [1].

The most serious complication in delayed diagnosis of DKA include hypertriglyceridemia acute pancreatitis (AP), cerebral edema, pulmonary edema, peripheral venous thrombosis, and rhabdomyolysis [1, 2].

Mild hypertriglyceridemia is a common complication found in improperly treated diabetes. Approximately 50% of patients with diabetic ketoacidosis (DKA) develop hypertriglyceridemia. Severe hypertriglyceridemia [TG > 22.4 mmol/L (> 1959 mg/dL)] was found in about 1–8% of adults with DKA. Only few cases have been reported in children with severity ranging from asymptomatic to severe acute pancreatitis. Severe hypertriglyceridemia, especially in patients with TG levels higher than 11.43––20.25 mmol/L (1,000–1,772 mg/dL), can increase risk of acute pancreatitis [1].

Several mechanisms affecting the appearance of hypertriglyceridemia have been proposed: increased free fatty acid (FFA) and amino acids secretion from adipocytes and muscle, increased counter-regulatory hormones causing increased gluconeogenesis and glycogenolysis in the liver. Elevated FFA taken up by the liver leads to increased production of very low-density lipoprotein (VLDL) which causes hypertriglyceridemia [3]. In patients with DKA, the clearance of VLDL and chylomicrons from plasma is restricted due to a transient decrease of lipoprotein lipase (LPL) activity, which is attributed to insulin deficiency. However, severe hypertriglyceridemia in DKA exceeding 22.6 mmol/L is less common (< 1%). It has been suggested that its pathogenesis may be exacerbated by a co-existing genetic predisposition to hyperlipidemia [4, 5]. Sever hypertriglyceridemia may result in mutations in genes encoding lipoprotein lipase (LPL), apolipoprotein C2 (APOC2), and apolipoprotein A5 (APOA5) caused by an autosomal recessive pattern of inheritance [5].

The objective of this case report is to present and describe the clinical features, laboratory investigations, case management, and natural course of hypertriglyceridemia in a 2-year-old girl with DKA.

CASE REPORT

We present a 2-year-old girl with a 2 weeks history of generalized weakness, polydipsia, polyuria, and vulval candidiasis. Past medical history was without health burden. Family history was negative for diabetes mellitus and hyperlipidemia.

She was admitted to the Emergency Department with clinical signs of DKA. Physical examination revealed signs of dehydration, including loss of skin turgor, dry mucous membranes, tachycardia, and hypotension (pulse rate 120/min, blood pressure 80/55 mm Hg, Kussmaul respirations). Hepatosplenomegaly was not observed. Anthropometric measurements showed weighed 13.6 kg (75 percentile) with a height of 92 cm (97 percentile).

Our patient was found to fulfill diagnostic criteria for DKA (pH 7.1, HCO^{3-} 8.8 mmol/L, BE -21.1 mmol/L), glucose level of 556 mg/dL. Initial biochemical analysis revealed hyperlipidemia [TG 11470 mg/dL (131.1 mmol/L)], serum sodium was 130mmol/L, potassium 4.3 mmol/L, amylase 28 U/L. Her blood demonstrated a grossly lipemic appearance. Its lipemic condition disturbed the results of other biochemical blood investigations.

At the Emergency Department, the patient was treated with intravenous infusion of insulin, fluid, and electrolyte replacement prior to transfer to our institution.

At our department, she was continued on intravenous fluid and intravenous infusions of insulin at a rate of 0.1 units/kg/hr. Breastfeeding was reduced. Over the ensuing days, the rate of the intravenous insulin infusion was gradually lowered. After 3 days of intensive intravenous infusions of insulin, she was transitioned to subcutaneous insulin. In the beginning we used multiple-daily insulin injections, afterward insulin pumps were being used daily dose [DD 3.8 (IU) unit of insulin, basal insulin — 1.2 IU].

Initial arterial blood showed a pH of 7,212, HCO^{3-} 11.5 mmol/L, BE -16.3 mmol/L, sodium 137 mmol/L, potassium 4.2 mmol/L, chloride 114 mmol/L. Additional blood tests showed a BUN of 22 mg/dL, creatinine 0.34 mg/dL, glucose 255 mg/dL, and hemoglobin A_{1C} 12.4%. Examination revealed a tired but interactive girl with dry oropharynx mucous membranes, clear lungs with Kussmaul respirations, tachycardia with a regular rhythm, a soft and tender epigastrium with hypoactive bowel sound.

Lipid profiles were analyzed on the second day of admission, with results revealing triglyceride of

Table 1. Triglycerides, total cholesterol, HDL, LDL and lipase during hospitalization

Hospital Day	TG (mmol/L)	Total cholesterol (mmo/L)	HDL (mmol/L)	LDL (mmol/L)	Lipase (units/L)
1	129.5	---	---	---	---
2	38.73	16.81	---	---	---
5	5.26	8.84	1	---	26
8	1.5	6.85	1.04	5.12	---

TG — triglycerides; HDL — high-density lipoprotein; LDL — low-density lipoprotein

3430 mg/dL, total cholesterol 650 mg/dL. The patient had no abdominal pain and serum lipase and amylase value were measured and found to be: lipase 26 units/L (reference range 0–31 units/L), amylase 28 units/L (reference range 22–80 units/L). Ultrasound of the abdomen did not reveal any abnormalities. Therefore, acute pancreatitis was excluded. Triglyceride level was reduced to 133 mg/dl within 7 days of admission (Tab. 1) without the use of anti-lipid medication.

Another laboratory findings were the blood-free T4 and TSH were normal at 0.75 ng/dL and 2,760 μIU/mL, and the evaluation for celiac disease was positive. At the time of diagnosis antibodies associated with type 1 diabetes including anti-GAD65 antibodies (375,79 U/mL, cutoff 10), IA-2 antibodies (451U/mL, cutoff 20) were strongly positive confirming a diagnosis of type 1 diabetes. ZnT8 antibodies (1.45 U/mL, cutoff 15) were negative. Since extremely high TG levels are frequently linked with loss of function mutations in the lipoprotein lipase gene (*LPL*) we did a detailed genetic analysis of this gene based on DNA extracted from whole blood. Molecular testing was performed by DNA Sanger sequencing using fluorescent-labeled terminating deoxynucleoside thisphosphates with gene-specific oligonucleotide primers and multiplex ligation-dependent probe amplification to detect exon deletions (MRC-Holland, Amsterdam, the Netherlands). We found two unlikely pathogenic heterozygous variants, one located in intronic sequence (rs11570891) and one in 3'UTR region (rs4922115), and both are frequent (> 10%) in a Polish general population. No severe mutation in the *LPL* gene was found.

Laboratory tests obtained 6 months after diagnosis showed a hemoglobin A1c of 6.1%, and normal fasting serum triglycerides of 116 mg/dL with total cholesterol 235 mg/dL.

DISCUSSION

We report a case of a patient with extreme, transient hypertriglyceridemia during DKA without mutations in genes affecting LPL. Diabetic lipemia is a serious complication of ketoacidosis involving significant morbidity and mortality. Its pathogenesis is not fully understood [5]. In DKA, the deficiency of insulin activates lipolysis in adipose tissue releasing increased FFA, which accelerates the formation of VLDL in the liver. In addition, reduced activity of lipoprotein lipase in peripheral tissue decreases removal of VLDL from the plasma, resulting in hypertriglyceridemia [6, 7]. Moderate hypertriglyceridemia is common during episodes of DKA [8]. However, severe hypertriglyceridemia, which is defined as a TG level > 2,000 mg/dL, is rare [7]. In these cases, co-existence of genetic mutations in lipoprotein lipase should be taken into account.

Phenotypic expression of heterozygous LPL mutations is variable. Patients with the absence of environmental stress may have a near-normal lipid profile. However, hyperinsulinemia and ketoacidosis overlap on heterozygous LPL deficiency may predispose to extreme hypertriglyceridemia [9].

Some patients with lipemia did have lipoprotein lipase deficiency. However, in contrast to published case reports describing diabetic lipemia, only one of six patients with lipemia had a loss-of-function LPL gene variant and none had APOC2 or GPIHBP1 gene mutations. The above data indicate that most cases of diabetic lipemia are secondary to a quantitative reduction of lipoprotein lipase, and a genetic mutation in LPL or its main cofactors has less impact on the pathogenesis of hypertriglyceridemia [5].

In severe hypertriglyceridemia, there is an increased risk of developing acute pancreatitis. Looking at the literature, it is clear that triglyceride levels can rise to high enough levels to significantly increase the risk of acute pancreatitis in individuals diagnosed with DKA, with reported triglyceride lev-

els from 11 to 100 mmol/L (962–8749 mg/dL). Two large series reported data in adult DKA with severe hypertriglyceridemia [10, 11]. Fulop and Eder found that 15 of 136 (11%) DKA patients had severe hypertriglyceridemia (TG > 1000 mg/dL), but only one patient developed acute pancreatitis. Incidence of severe hypertriglyceridemia was similarly found in 8 of 100 (12.5%) adult DKA patients in the other of the two studies, with half of the patients developing acute pancreatitis. In children, most cases were individually presented inpatient case reports. All reported cases had TG levels higher than 1000 mg/dL, supporting the hypothesis that elevated TG (> 1000 mg/dL) is a risk factor for acute pancreatitis. However, 3 out of 11 patients (2.8%) did not develop acute pancreatitis. Our patient did not develop acute pancreatitis although she had an extremely high TG level (11,470 mg/dL), similarly to a published case report describing pediatric patient who did not develop acute pancreatitis, even though he had an extremely high TG level (14,461 mg/dL) [11]. As such, other risk factors for this condition need to be identified. Accordingly, clinical investigations for acute pancreatitis should be routine in all cases presenting with TG levels higher than 1000 mg/dL to ensure early and proper management.

We suggest that pathogenesis of lipid profiles disturbances in DKA in our patients may be exacerbated by co-existing additional factors like breast-feeding, which is associated with increased mean total cholesterol (TC) and LDL levels [12, 13].

In the present case hypertriglyceridemia during ketoacidosis improved with intravenous fluid and insulin administration according to DKA guidelines, because the major mechanism of hypertriglyceridemia is insulin deficiency. Plasma TG level was gradually reduced to 133 mg/dL within 7 days without using lipid-lowering agents. In most cases, with diabetic hypertriglyceridemia plasma, TG level reduced within 3–17 days. However, 9 of 15 patients reviewed by Fulop and Eder had normal plasma TG concentrations for up to 6 months without any lipid-lowering agent.

In our case, the rapid normalization of triglyceride levels with insulin replacement goes against heritable dyslipidemia. The deficiency of lipoprotein lipase in patients with a history of diabetic lipemia was mainly quantitative and not secondary to the mutation in LPL.

CONCLUSIONS

The pathogenesis of diabetic lipemia is varied. It can be caused by profound insulin deficiency, severe hypertriglyceridemia may be caused by mutations in genes encoding lipoprotein lipase (LPL) and an additional factor which should be taken into consideration in very young children is breast-feeding, which is associated with increased mean total cholesterol (TC) and LDL levels.

Conflict of interest

All authors declare no conflict of interest.

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