Hypertriglyceridemia with acute pancreatitis in a 14-year-old girl with diabetic ketoacidosis

Running title: Hypertriglyceridemia with acute pancreatitis in diabetic ketoacidosis

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**ABSTRACT**

Diabetic ketoacidosis (DKA) is a medically fatal condition in poorly controlled hyperglycemia or newly diagnosed diabetes mellitus. Severe hypertriglyceridemia (HTG) is an uncommon complication of DKA and can be associated with acute pancreatitis (AP). We present the clinical manifestations, laboratory findings, and management of AP associated with HTG in a 14-year-old girl with DKA. The patient with seven-year history of type 2 diabetes presented with epigastric pain, 1 month after stopping insulin injection. DKA, severe HTG, and AP were diagnosed based on the laboratory and imaging tests. She recovered from DKA after conventional treatment for DKA, and her triglyceride (TG) level was reduced from 10,867 mg/dL to normal range after 6 days of admission without anti-lipid medication. Considering not too low C-peptide levels, negative diabetes-related antibodies and high TG level, targeted gene panel sequencing was performed on the genes associated with diabetes and HTG. We identified a heterozygous mutation c.4607C>T (p. Ala1537Val) in ABCC8 related to maturity-onset diabetes of the young (MODY) 12. This is the first reported case of HTG induced AP with DKA in a patient with MODY. In addition, we reviewed the literatures for pediatric cases of HTG with DKA. In patients with DKA, timely awareness of severe HTG related to insulin deficiency is crucial for improving the consequence of AP. We recommend considering AP in all DKA patients presenting with severe HTG to ensure early and proper management.

**Keywords:** hypertriglyceridemia, acute pancreatitis, diabetic ketoacidosis
INTRODUCTION

Diabetic ketoacidosis (DKA) is a medically fatal condition in poorly controlled hyperglycemia or newly diagnosed diabetes mellitus (DM). Cerebral edema is its most devastating complication and consists of more than 20% mortality of DKA cases \(^1\). Severe hypertriglyceridemia (HTG, triglyceride [TG] > 1,000 mg/dL) is an uncommon complication of DKA and can be associated with acute pancreatitis (AP) \(^2\). The combination of DKA, HTG, and AP has been discussed in adults. While severe HTG was identified in around 8% of DKA in adults, data of this combination in children were limited \(^3,4\). Here, we present the clinical manifestations, laboratory findings, and management of AP associated with HTG in a 14-year-old girl with DKA. In addition, literature on HTG with DKA in pediatric cases was reviewed.

CASE REPORT

A 14-year-old girl presented to our hospital owing to severe epigastric pain, nausea, and fever for one day. She was diagnosed with type 2 DM at another hospital at the age of 7 years and 10 months, when HbA1c was 10.1% and postprandial C-peptide was 7.2 ng/mL, while her diabetes-related antibodies were all negative. She was treated with metformin (up to 2 g/day) in the early stage of DM; however, basal insulin (glargine) was added to metformin owing to the poor control of hyperglycemia (HbA1c level, 14.0%). It was one month before this episode that she discontinued blood glucose tests and regular insulin injection. When presented to our hospital her mental status was alert and vital signs revealed blood pressure 132/70 mmHg, heart rate 157/min, respiratory rate 24/min, and body temperature 38.2°C. Her
body weight, height and body mass index (BMI) showed 60.1 kg (standard deviation score [SDS], 1.18), 157.4 cm (SDS, -0.07), and 24.3 kg/m² (SDS, 1.38), respectively. She showed a dry mouth and decreased skin turgor. Her abdomen was soft and distended, and the bowel sounds were normal. She complained of tender epigastrium on palpation. Laboratory findings were suggestive of DKA: glucose level of 311 mg/dL, venous blood gas with a pH of 7.2, pCO₂ of 21 mmHg, HCO₃⁻ of 8.2 mmol/L and base excess of -17.8 mmol/L, and β-hydroxybutyrate level of 3.4 mmol/L (normal reference < 0.4-0.5 mmol/L). The HbA1c level was 14.2% and urinalysis revealed 3+ glucose and 3+ ketones. Other laboratory findings presented the following results: white blood cell count, 12,380/μL; hemoglobin level, 13.5 g/dL; platelet count, 205,000/μL; total cholesterol level, 336 mg/dL; high-density lipoprotein (HDL) level, 14 mg/dL; TG level, 10,867 mg/dL; low-density lipoprotein (LDL) level, 32 mg/dL; aspartate aminotransferase level, 16 U/L; alanine aminotransferase level, 19 U/L; amylase level, 711.4 U/L (normal reference, 28-100 U/L); lipase level, 2,403.2 U/L (normal reference, 13-60 U/L); sodium level, 133 mmol/L; potassium level, 3.9 mmol/L; chloride level, 97 mmol/L; and C-reactive protein (CRP) level, 1.61 mg/dL. Anti-glutamic acid decarboxylase antibody and anti-insulin auto antibody tests were negative. Eruptive xanthoma or xanthelasma was not observed. There were no abnormalities such as lipemia retinalis in an ophthalmologic examination. Abdominal computed tomography (CT) revealed a diffuse edematous pancreas with adjacent fluid collection, which suggested AP grade D (Fig. 1A). In addition, she had a fatty liver. No gallbladder involvement was seen.

Immediate management included intravenous rehydration therapy, continuous intravenous insulin infusion (6 units/hour), experimental antibiotics (piperacillin and tazobactam) for AP, and an analgesic (propacetamol, 1 g) for pain control. On the second day of admission, CRP
level increased to 33.47 mg/dL and abdominal pain persisted. She did not complain of steatorrhea. Follow-up CT of the abdomen showed an increased volume of peripancreatic fluid collection relative to the previous examination suggesting AP grade D (Fig. 1B). Antibiotics were changed to broad-spectrum antibiotics (meropenem and vancomycin). Four days after admission, her TG level declined to 305 mg/dL, and CRP level was 16.41 mg/dL. Abdominal pain was resolved. Blood culture was negative, and antibiotics were changed to piperacillin and tazobactam. She recovered from DKA, and TG decreased to 197 mg/dL without anti-lipid medication after 6 days of admission. Because her abdominal pain had resolved and the serum amylase and lipase were nearly normal (27.2 and 68 U/L, respectively), she commenced a normal diet. Repeated ultrasonography showed resolution of pancreatic inflammation. She did not have complications of diabetes including retinopathy, nephropathy, and neuropathy. Serial laboratory results related with HTG and AP during hospitalization were summarized in Table 1.

Considering not too low C-peptide levels, negative diabetes-related antibodies and high TG level, targeted gene panel sequencing was performed on the genes associated with diabetes and HTG. With informed consent from the patient, DNA was isolated from the peripheral blood leukocyte using the chemagic™ Magnetic Separation Module I (MSM I) method (PerkinElmer chemagen, Baesweiler, Germany). 57,000 target exons of a total of 4,503 clinically relevant genes were captured by xGen Inherited Disease Panel (Integrated DNA Technologies, Inc., Coralville, Iowa, USA) and sequenced with NextSeq500 platform (Illumina) for 2 × 150 bp paired-end reads, which were mapped to the hg19 utilizing the Burrow–Wheeler Aligner (BWA version 0.7.12). For local realignment, recalibration, and variant calling, the Genome Analysis Tool Kit (GATK version 3.5) was used. We identified a
heterozygous variant c.4607C>T (p. Ala1537Val) in exon 38 of the ATP-binding cassette transporter sub-family C member 8 (ABCC8) for maturity-onset diabetes of the young (MODY) 12, and no pathogenic variant was detected in other genes. The missense variant c.4607C>T (p.Ala1537Val) is a variant of unknown significance (VUS) based on the American College Medical Genetics and Genomics (ACMG) guidelines (Richards et al., 2015). This variant was found at a frequency of 0.0008% in the population database (gnomAD) and classified as “Uncertain significance” in ClinVar. This variant was predicted to be “damaging” by algorithms developed to predict the effect of missense changes on protein structure (SIFT, Polyphen2, and MutationTaster). Generally, family segregation analysis can determine the pathogenicity of a VUS. Regrettably, her family members were not readily available for genetic testing and clinical information. After discharge, she took basal insulin before breakfast and insulin aspart thrice a day before meals.

DISCUSSION

This case emphasizes the necessity for recognition of AP associated with severe HTG in patients with DKA. DKA represents severe insulin deficiency characterized by hyperglycemia and metabolic acidosis with ketone accumulations 5). The clinical presentations and complications of DKA result from hyperglycemia, dehydration, ketosis, and electrolyte imbalance. HTG in DKA is attributed to insulin deficiency, leading to increased lipolysis. Consequently, free fatty acid (FFA) is released, that activates synthesis of very low-density lipoprotein (VLDL) 6,7). Lipoprotein lipase (LPL) is responsible for the removal of VLDL and chylomicrons from the bloodstream. Insulin deficiency leads to decreased LPL activity, which causes HTG 8). Severe HTG is rare; however, it is an

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important risk factor for AP). Pancreatic lipase hydrolyzes TG, inducing production of FFA, which activates trypsinogen and causes autodigestion of the pancreatic gland. Major treatments of severe HTG include insulin, heparin and plasmapheresis; however, there are few studies specifically in children and adolescents. Maintaining a TG level < 500 mg/dL is believed to result in symptom improvement. Insulin activates LPL, facilitating of degradation and clearing of TG. Heparin leads to the release of LPL from the endothelial cells, resulting in TG degradation. Oral anti-lipid medications are recommended when patients are capable of an oral diet, and fibrates can lower TG levels by 40-60%. In a routine practice, the Friedewald equation is used to estimate LDL (total cholesterol (mg/dL) - HDL (mg/dL) - TG (mg/dL)/5). It has been believed that LDL is not exactly estimated when TG level exceeds 400 mg/dL. Generally, the Friedewald equation works properly in normolipidemia, not hyperlipidemia. Thus, there is a discrepancy between estimated LDL by the equation and actual measurements in our case. Published pediatric cases of AP associated with HTG in DKA are summarized in Table 2. All reports showed that severe HTG is an identifiable risk factor for AP. TG levels gradually decreased to below 500 mg/dL after 1-14 days after management. In our patient, hydration and insulin infusion resulted in resolution of DKA and concurrent normalization of HTG. Initial lipid profiling is important in patients with DKA, because it can be a clue for timely abdominal imaging to diagnosis of AP. Moreover, abdominal pain is a common presentation of DKA as well as AP, with the symptom reported in nearly 50% of the cases and related to variable gastrointestinal manifestations.

The ABCC8 gene, encoding the sulfonylurea receptor 1 subunit of ATP-sensitive potassium (K\textsubscript{ATP}) channel can regulate secretion of insulin. ABCC8 mutations have been shown to cause congenital hyperinsulinism (CHI), type 2 DM, gestational DM, neonatal diabetes and MODY.
CHI is associated with blindness of pancreatic β-cells responsible for insulin secretion, causing severe and persistent hypoglycemia. CHI is classified histologically into diffuse hyperinsulinism or focal islet-cell hyperplasia. Diffuse hyperinsulinism is caused by an autosomal recessive manner and entire β-cells in the pancreas are affected. On the other hand, focal form is heterozygous paternally inherited K$_{ATP}$ mutation of chromosome 11p15 region, which is confined to the islet cells of focal lesion. It is challenging to differentiate MODY from other diabetes depending on clinical manifestations. In patients with MODY, β-cell function is generally conserved, and insulin is not required in the early stage of the disease. Kapoor et al. reported a dominant ABCC8 mutation, A1537V, identified in our patient, which causes asymptomatic carrier, hyperinsulinemic hypoglycemia and gestational DM within three generations of one family. Mutations in ABCC8 mutations associated with both hyperactivity and underactivity of the K$_{ATP}$ channel. Slow and progressive damage to β-cells owing to increased β-cell apoptosis can lead to both remission of hyperinsulinism and progression to diabetes. Considering the clinical variability of ABCC8 mutations, the mutation identified in our patient is suspected to be related to MODY. As the result of target gene penal sequencing was classified as a VUS, family segregation analysis can enforce the pathogenicity of this variant. However, it was not available to collect the detailed family history and conduct genetic test for a personal matter. This is the limitation of our case and thus, further validations in additional patients and functional study are needed to prove the pathogenicity of this variant. Patients with MODY respond to sulfonylurea therapy. Thus, switching from insulin to sulfonylurea is under consideration in our patient.
In this study we presented a 14-year-old girl with AP related to severe HTG in DKA. This is the first report of HTG induced AP with DKA in a patient with MODY. In patients with DKA, timely awareness of severe HTG related to insulin deficiency is crucial for improving the consequence of AP. Based on our experience and the review of pertinent literature, we recommend considering AP in all DKA patients presenting with severe HTG to ensure early and proper management.

**Ethical statement**

Informed consent was obtained from the parents of the patient.

**Conflicts of interest**

No potential conflict of interest relevant to this article was reported.

**Acknowledgement**

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References


13. Lin L, Quan H, Chen K, Chen D, Lin D, Fang T. ABCC8-Related Maturity-Onset


Fig. 1. Contrast-enhanced abdominal CT imaging. The initial CT scan shows edematous pancreas (arrowhead) and adjacent fluid collection (arrow), suggesting grade D acute pancreatitis. (A) axial image, (B) coronal image.

Table 1. Serial laboratory results.

TG Triglyceride, TC Total cholesterol, HDL High-density lipoprotein, LDL Low-density lipoprotein, CRP C-reactive protein.

Table 2. Pediatric cases of AP associated with HTG in DKA
Acute pancreatitis, Hypertriglyceridemia, Diabetic ketoacidosis, Triglyceride, not available.
Table 1. Serial laboratory results.

<table>
<thead>
<tr>
<th>Hospital Day</th>
<th>TG (mg/dL)</th>
<th>TC (mg/dL)</th>
<th>HDL (mg/dL)</th>
<th>LDL (mg/dL)</th>
<th>Amylase (U/L)</th>
<th>Lipase (U/L)</th>
<th>CRP (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>At admission</td>
<td>10,867</td>
<td>336</td>
<td>14</td>
<td>32</td>
<td>711.4</td>
<td>2,403.2</td>
<td>1.61</td>
</tr>
<tr>
<td>9 hours after admission</td>
<td>4,589</td>
<td>559</td>
<td>13</td>
<td>25</td>
<td>734.9</td>
<td>1,787.9</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>652</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>180.9</td>
<td>401.5</td>
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<tr>
<td>4</td>
<td>305</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>59.4</td>
<td>107.2</td>
</tr>
<tr>
<td>7</td>
<td>197</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>27.2</td>
<td>68</td>
</tr>
<tr>
<td>10</td>
<td>227</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>40.4</td>
<td>114.2</td>
</tr>
</tbody>
</table>

TG Triglyceride, TC Total cholesterol, HDL High-density lipoprotein, LDL Low-density lipoprotein, CRP C-reactive protein.
Table 2. Pediatric cases of AP associated with HTG in DKA

<table>
<thead>
<tr>
<th>Cases</th>
<th>Age (years)</th>
<th>Peak TG (mg/dL)</th>
<th>Peak Amylase (U/L)</th>
<th>Peak Lipase (U/L)</th>
<th>Management with anti-lipid medication</th>
<th>Time to normal TG (days, [TG level])</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cywinski et al., 1965 18)</td>
<td>12</td>
<td>&gt;1,000</td>
<td>175</td>
<td>NA</td>
<td>No</td>
<td>7 (232)</td>
</tr>
<tr>
<td>Slyper et al., 1994 19)</td>
<td>14</td>
<td>3,119</td>
<td>627</td>
<td>3,680</td>
<td>No</td>
<td>NA</td>
</tr>
<tr>
<td>Hahn et al., 2010 9)</td>
<td>20</td>
<td>15,000</td>
<td>443</td>
<td>615</td>
<td>No</td>
<td>3 (506)</td>
</tr>
<tr>
<td>Lutfi et al., 2012 5)</td>
<td>10</td>
<td>16,334</td>
<td>NA</td>
<td>3,537</td>
<td>Fenofibrate, plasmapheresis</td>
<td>1.5 (1,100)</td>
</tr>
<tr>
<td>Aboulhosn and Arnason, 2013 20)</td>
<td>18</td>
<td>1,724</td>
<td>319</td>
<td>NA</td>
<td>No</td>
<td>NA</td>
</tr>
<tr>
<td>Wolfgram and Macdonald, 2013 3)</td>
<td>10</td>
<td>8,300</td>
<td>NA</td>
<td>2,950</td>
<td>No</td>
<td>NA</td>
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<tr>
<td>Animesh A Singla et al., 2015 8)</td>
<td>19</td>
<td>4,009</td>
<td>408</td>
<td>1,714</td>
<td>Fenofibrate</td>
<td>1 (NA)</td>
</tr>
<tr>
<td>Sharma, PK et al., 2017 5)</td>
<td>4</td>
<td>13,846</td>
<td>150</td>
<td>442</td>
<td>No</td>
<td>28 (90)</td>
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<tr>
<td>Fatima Zahra Zaher et al., 2019 7)</td>
<td>14</td>
<td>6,400</td>
<td>NA</td>
<td>1,000</td>
<td>Fenofibrate, unsaturated oils</td>
<td>7(332)</td>
</tr>
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<tr>
<td>Yagnik et al., 2019</td>
<td>16</td>
<td>2,515</td>
<td>612</td>
<td>5,387</td>
<td>Fenofibrate</td>
<td>14 (170)</td>
</tr>
<tr>
<td>Our case</td>
<td>14</td>
<td>10,867</td>
<td>711.4</td>
<td>2,403.2</td>
<td>No</td>
<td>6 (197)</td>
</tr>
</tbody>
</table>

Fig. 1. Contrast-enhanced abdominal CT imaging. The initial CT scan shows edematous pancreas (arrowhead) and adjacent fluid collection (arrow), suggesting grade D acute pancreatitis. (A) axial image, (B) coronal image.