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Euglycemic diabetic ketoacidosis associated metabolic encephalopathy caused by dapagliflozin: a rare case report

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Abstract

Background Sodium–glucose cotransporter-2(SGLT-2) inhibitors are a newer class of antidiabetic drugs with the increased risk of euglycemic diabetic ketoacidosis(EuDKA). Encephalopathy is a rare but life-threatening event of EuDKA. Due to paradoxically normal or slightly elevated serum glucose levels, it's easy to be mimicked by cerebral infarction, structural brain damage, thus leading to delayed diagnosis and causing seriously irreversible brain injury.

Case presentation We report severe EuDKA with metabolic encephalopathy secondary to dapagliflozin in a type 2 diabetes mellitus(T2DM) patient.A 72-year-old female was found unconscious 70 minutes ago.Laboratory evaluation revealed a severe metabolic acidosis with an elevated anion gap, and ketones were elevated in the blood and positive in the urine. The patient was eventually diagnosed with metabolic encephalopathy associated with EuDKA and managed accordingly.

Conclusions Metabolic encephalopathy is a rare but life-threatening complication of EuDKA caused by SGLT-2 inhibitors, the imaging features are similar to those of other metabolic encephalopathy such as poisoning and hypoxia. The precise pathogenesis of encephalopathy in EuDKA remains poorly understood, potentially resulting from the toxic consequences of electrolyte disturbances, ketosis, and acidosis.Testing the level of ketones is essential for unconscious patients who are taking SGLT-2 inhibitors.

Keywords Dapagliflozin, Euglycemic diabetic ketoacidosis, Metabolic encephalopathy, Sodium–glucose cotransporter-2 inhibitors, Case report

Introduction

SGLT-2 inhibitors are a new class of oral hypoglycemic drugs, one of the most widely used medications is dapagliflozin. EuDKA, a serious and potentially life-threatening acute complication of diabetes mellitus, with a mortality rate 1.5% [1], occurs with normal or mildly elevated blood glucose(< 14 mmol/L), and is commonly defined as the presence of ketosis and metabolic acidosis [2]. An increasing number of reports have demonstrated the association between SGLT-2 inhibitors and EuDKA [3, 4]. The possible mechanisms by which SGLT-2 inhibitors cause EuDKA are intricate and uncertain. SGLT-2

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inhibitors decrease serum glucose primarily by promoting excretion and inhibiting glucose reabsorption in urine. The loss of urinary glucose results in a state of carbohydrate starvation and volume depletion, increasing the glucagon/insulin ratio and leading to severe dehydration and ketosis [5]. Decreasing insulin release combined with high levels of competitive hormones including glucagon, cortisol and catecholamines accelerates the conversion of fatty acids to ketone bodies [1]. SGLT-2 inhibitors also reduce ketone clearance [6]. Eventually, there will be a buildup of ketosis in the presence of lower glucose levels. EuDKA is not always observed in patients taking SGLT-2 inhibitors; possible precipitants and risk factors include underlying autoimmune diabetes in adults (LADA), surgery, low carbohydrate diet, insulin withdrawal or dose reduction, dehydration, excessive exercise, heavy alcohol intake, etc [7, 8]. Currently, there are few reports on EuDKA-associated metabolic encephalopathy, and its imaging characteristics remain unclear.

In this report, our objective was to present a case of a patient with T2DM who was admitted to the emergency department with complaints of coma. Through analysis of clinical symptoms, imaging features, and disease triggers, the patient was ultimately diagnosed with EuDKA-related metabolic encephalopathy induced by SGLT-2 inhibitors.

Table 1 Inpatient laboratory values

Laboratory aassessments	Result	Referrnce
Serum glucose, (mmol/L)	13. 3	3. 3–6. 1
White blood cell, (*10^9/L)	17. 4	17. 4
Hemoglobin, (g/L)	160	115–150
Hs-CRP, (mg/L)	52. 0	0–8
D-dimer, (ng/mL)	3291	0-500
Uric acid, (μmol/L)	739	150–350
Urea nitrogen, (mmol/L)	16. 0	1. 7–8. 3
Creatinine, (μmol/L)	110	40–110
Serum potassium, (mmol/L)	3. 95	3. 5–5. 3
β-hydroxybutyrate, (μmol/L)	8474	30–300
[#]Urine ketones	++	-
Lactic acid, (mmol/L)	1. 4	1. 0–2. 5
HbA1c, (%)	12	4–6
PH	7. 243	7. 35–7. 45
Bicarbonates, (mmol/L)	12. 7	22–27
Anion gap, (mmol/L)	22. 6	8–16
Osmotic pressure, (osmo/kg)	283	280–320
[##]CSF cell count, (/μ)	0	-
[##]CSF protein, (mmol/L)	6.0	15.0–45.0

Abbreviation: HbA1c: glycosylated hemoglobin. Hs-CRP: high-sensitivity C-reactive protein.CSF: Cerebrospinal fluid.[#]: Urine specimen.[##]: Cerebrospinal fluid specimen. All other results are derived from serum samples

Case presentation

A 72-year-old female with T2DM presented to our Emergency Department and was discovered to have been in a coma for 70 min prior to her arrival. Living alone, the patient and her family members typically communicated via telephone. In the past week, she hadn't complained to her family about the following conditions, including fever, nausea, vomiting, abdominal pain, diarrhea, reduced appetite, substance abuse, or alcohol consumption. She has had T2DM for the past 10 years, previously treated with a combination of Dapagliflozin 10 mg once daily and Acarbose 100 mg twice daily, with subcutaneous insulin injection twice daily being added to the regimen 10 days ago. She adhered to a regular insulin injection schedule and had no history of liver disease. Vital signs at presentation were: temperature 36.6 °C, pulse rate 102 beats/min, respiratory rate 18breaths/min, blood pressure 175/86 mmHg. Physical examination with no obvious Kussmaul breathing and dehydration. The pupil diameter and light reflexes were in the normal range. Besides hypermyotonia of extremities, no other focal neurologic deficits were observed.

Laboratory and imaging assessments

Blood test results indicated a potential concurrent infection, while arterial blood gases revealed severe metabolic acidosis with an elevated anion gap (pH 7.243, bicarbonates 12.7 mmol/L, anion gap 22.6 mmol/L). Elevated levels of β-hydroxybutyrate at 8.474 mmol/L and positive ketonuria were also observed. Detailed results are shown in Table 1.

The findings from the cranial magnetic resonance imaging (MRI) are depicted in Fig. 1: Panels a and b show low signal changes in the bilateral basal ganglia and hippocampal regions on ADC (Apparent Diffusion Coefficient) images (black arrows); Panels c and d show high signal changes on DWI (Diffusion Weighted Imaging) (white arrows); Panels e and f show slightly high signal changes on FLAIR (Fluid-Attenuated Inversion Recovery) images (white arrows).

Treatment

At our institution, due to the inability to completely rule out cerebral infarction, we administered intravenous thrombolytic treatment using a 36 mg dose of alteplase. However, there was no improvement in symptoms. The patient was subsequently transferred to a tertiary hospital where they were diagnosed with metabolic encephalopathy associated with EuDKA. She was promptly admitted to the intensive care unit (ICU), with a low-dose insulin infusion to manage hyperglycemia, glucose supplementation to prevent hypoglycemia, and administration of mannitol to reduce intracranial pressure. Given the elevated inflammatory markers and the initial uncertain

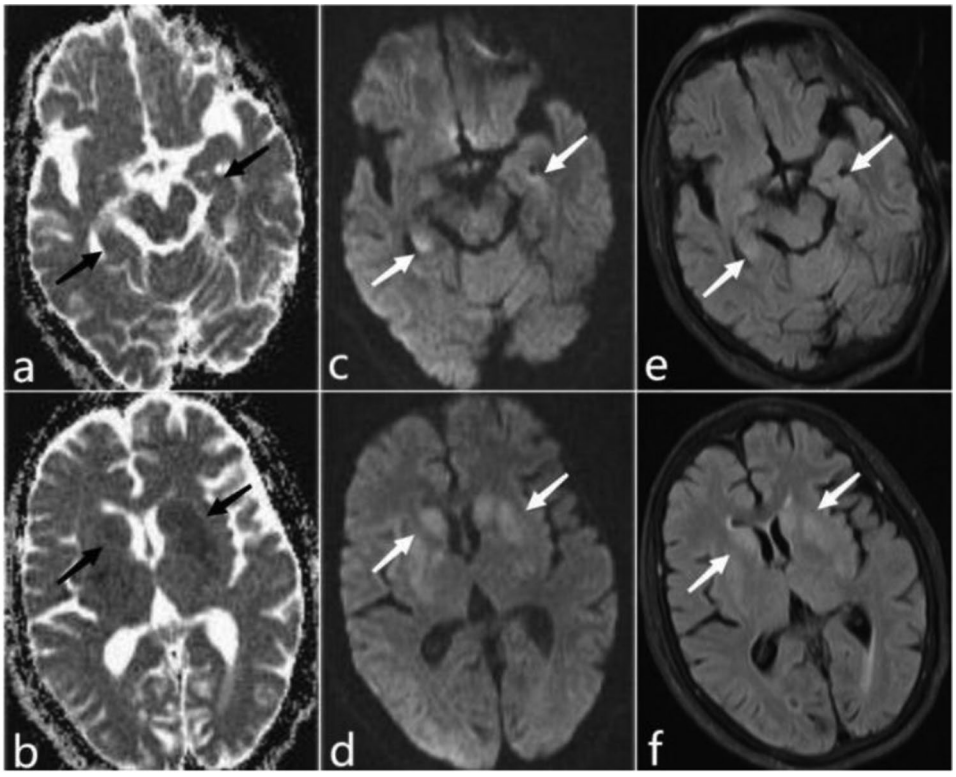

Fig. 1 Panels **a** and **b** show low signal changes in the bilateral basal ganglia and hippocampal regions on ADC (Apparent Diffusion Coefficient) images (black arrows); Panels **c** and **d** show high signal changes on DWI (Diffusion Weighted Imaging) (white arrows); Panels **e** and **f** show slightly high signal changes on FLAIR (Fluid-Attenuated Inversion Recovery) images (white arrows)

infection, empirical antimicrobial therapy with cefoperazone/sulbactam was used. Following this treatment, serial blood gas analyses showed gradual resolution of her ketoacidosis. During the hospitalization, the patient's follow-up magnetic resonance imaging (MRI) did not reveal any new cerebral infarctions, and the number of lesions remained unchanged compared to previous assessments. However, upon discharge, the patient still exhibited sluggish cognitive responses, which may be related to brain injury and requires longer-term follow-up.

Discussion

We report a case of altered mental status in a patient with type 2 diabetes treated with dapagliflozin. Only several reports of disturbance of consciousness with dapagliflozin have been documented and triggered in different scenarios [9–11]. The patient's serum β-hydroxy butyrate was 8474 μmol/L, nearly 30 times higher than normal. Blood sugar was found to be mildly elevated (12.8 mmol/l) and PH was 7.243. The patient's family withheld consent for cerebrospinal fluid immune antibody testing. Despite this limitation, a thorough diagnostic workup was performed, which included a detailed analysis of imaging findings and the exclusion of diverse neurological disorders such as poisoning, seizures, tumors, cerebrovascular accidents, and central infections. Based on these comprehensive evaluations, a definitive diagnosis of euglycemic diabetic ketoacidosis (EuDKA)-associated metabolic encephalopathy was confirmed.Metabolic encephalopathy refers to diffuse or focal brain dysfunction which is attributed to impaired brain metabolism in the absence of primary structural dysfunction [12]. The augmented β-hydroxybutyric acid and acidemia play key roles in the upregulation of vascular endothelial growth factor expression and indirectly increasing cerebral vascular permeability [13], resulting in brain edema and dysfunction. The limited clinical experience and ambiguous MRI features led us to a misdiagnosis of cerebral infarction, resulting in unnecessary thrombolysis treatment. Despite the absence of bleeding and other complications, delayed diagnosis and treatment imposed a significant economic burden on the patient.

Symptoms of EuDKA, similar to Diabetic Ketoacidosis(DKA), usually include nausea, vomiting, abdominal pain, polyuria, polydipsia, weight loss, dehydration, weakness, fatigue, tachycardia, dyspnea and Kussmaul breathing. Mental states range from awakeness to deep lethargy or coma [14–16]. The MRI findings in this patient are consistent with the characteristic features of metabolic encephalopathy (Fig. 1). Identical with poisoning and hypoxia metabolic encephalopathy, it involves

multiple sites, including bilateral basal ganglia, cortex, and periventricular white matter (PVWM) [17].

Treatment for EuDKA parallels that of DKA except that the risk of relapse into DKA is high in the setting of SGLT-2 inhibitor use [15]. Infused insulin is a major therapeutic tool for EuDKA, other management measures covering aggressive rehydration, glucose supplementation, and correction of electrolyte imbalance, as well as control of precipitating factors [18]. Severe acidosis may require bicarbonate therapy [14]. Resolution of EuDKA is defined as pH > 7.3, bicarbonate > 15.0 mmol/L, and serum ketones < 0.6 mmol/L. In a retrospective study, EuDKA patients experienced a 5.9-hour reduction in insulin infusion time but had more than three times the frequency of hypoglycemia compared to those with DKA [19]. Hence, When the blood gluose level falls below 250 mg/dl, the insulin infusion rate should be reduced and dextrose can be added to the intravenous fluids to avoid hypoglycemia [14]. Other studies [20] have also indicated that in the treatment of EuDKA, approximately 61.5% of patients required intensive care, with some needing organ protection treatment such as invasive mechanical ventilation (13%), vasopressors (6.5%), or renal replacement therapy (5.9%). The overall mortality rate was 2.4%. The diagnostic dilemma of EuDKA portends worse outcomes compared with classic DKA.

Conclusions

Metabolic encephalopathy is a rare but life-threatening complication of EuDKA caused by SGLT-2 inhibitors, the imaging features are similar to those of other metabolic encephalopathy such as poisoning and hypoxia. The precise pathogenesis of encephalopathy in EuDKA remains poorly understood, potentially resulting from the toxic consequences of electrolyte disturbances, ketosis, and acidosis. For unconscious patients with taking SGLT-2 inhibitors, commonly testing the level of ketones and magnetic resonance imaging of the brain are essential.

Abbreviations

EuDKA	Euglycemic Diabetic Ketoacidosis
SGLT-2	Sodium-Glucose Cotransporter-2
T2DM	Type 2 Diabetes Mellitus
DKA	Diabetic Ketoacidosis
LADA	Latent Autoimmune Diabetes In Adults
PVWM	Periventricular White Matter
MRI	Magnetic Resonance Imaging
HS-CRP	High-Sensitivity C-Reactive Protein
HBA1C	Hemoglobin A1c
CSF	Cerebrospinal fluid

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Author contributions

L. L. C. , Z. H. X. , G. S. Y. , R. Z. M. , W. L. S. collected data, searched the literature, and wrote case reports. L. L. C. , Z. H. X. , G. S. Y. were in charge of conducting the final review and making modifications to the manuscript.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

The patient gave written consent for their personal or clinical details along with any identifying images to be published in this study.

Competing interests

The authors declare no competing interests.

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