



# Ketoacidotic crisis after vaccination in a girl with beta-ketothiolase deficiency: a case report

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**Abstract:** Beta-ketothiolase (mitochondrial acetoacetyl-CoA thiolase, T2) is a rare autosomal recessive disease caused by ACAT1 gene pathogenic variant involving isoleucine catabolism and ketone body metabolism disorder. The onset of ketoacidotic crisis commonly follows prior concurrent diseases or triggers including long-time fasting, infections, intake of high-level of lipids or proteins, etc. A girl aged 8 months presented with fever and cough on the day after vaccination of the second dose of Japanese encephalitis inactivated; on the second day after vaccination, she was admitted to the local hospital because of unconsciousness and dyspnea. After 1 day of treatment at the local hospital, she was referred to our hospital due to exacerbated conditions including unconsciousness and convulsion. When referring to our hospital, she had metabolic acidosis, hypokalemia, hypernatremia, hyperammonemia, and a Glasgow coma scale of 8 and Kussmaul breathing. Five percent NaHCO<sub>3</sub> (24 mL/kg), glucose and insulin (4–6 g glucose/1 U insulin) were continuously infused for correcting acidosis. L-carnitine (350 mg/kg/day) was given for ensuring the energy and increasing exudates of metabolites after admission. Protein was limited at 1.5 g/kg/day. Mechanical ventilation support and hemodialysis were used. The patient was still under unconsciousness after 2 weeks of intensive treatment in the Pediatric Intensive Care Unit (PICU). Due to her severe illness, the child's parents ultimately decided to redirect their goals of care, and the child was discharged home where she died. For children with acute unexplainable metabolic acidosis, differential diagnosis of T2 deficiency should be considered. Rigorous indicative treatments including mechanical ventilation and hemodialysis should be given timely if ketoacidotic crisis occurred in patients with T2 deficiency.

**Keywords:** Ketoacidotic crisis; vaccination; beta-ketothiolase deficiency; case report

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## Introduction

Beta-ketothiolase (mitochondrial acetoacetyl-CoA thiolase, T2) is a rare autosomal recessive disease caused by *ACAT1* gene pathogenic variant involving isoleucine catabolism and ketone body metabolism disorder (1-4). Clinical presentations vary in patients with beta-ketothiolase deficiency from mild or no symptoms to severe recurrent episodes of ketoacidotic crises. The triggers to ketoacidotic crises include long-time fasting, infections, intake of high-level of lipids or proteins,

etc. (4). Characteristic laboratory findings include significant ketonuria, increased urine 2-methyl-3-hydroxybutyric acid (2M3HB), 2-methylacetoacetic acid (2MAcAc), and tiglylglycine (TG), and elevated blood levels of tiglylcarnitine (C5:1) and 2-methyl-3-hydroxybutyryl-carnitine (C5-OH) carnitines (2-4).

For pediatricians, T2 deficiency should be considered as a differential diagnosis in patients with severe metabolic acidosis even in regions where T2 deficiency is covered by newborn screening (NBS) program (4). Herein, we aimed to

report a case of T2 deficiency with ketoacidotic crisis after vaccination against Japanese encephalitis. We also reviewed the literature and focused on discussing the triggers of ketoacidotic crises in T2 deficiency and how to prevent and manage ketoacidotic crisis in these patients.

We present the following article in accordance with the CARE reporting checklist (available at <http://dx.doi.org/10.21037/tp-20-265>).

## Case presentation

An 8-month-old female infant was admitted to this hospital because of unconsciousness and convulsion.

The patient has been well until 3 days before this admission, when fever and cough occurred on the day after vaccination of the second dose of Japanese encephalitis inactivated. Antipyretic and cough medicine were administered to the patient. On the second day, the patient developed to unconsciousness and dyspnea suddenly at home. She was then admitted to the local hospital in emergency. Laboratory examination revealed a severe metabolic acidosis (pH =6.98, BE = -28 mmol/L, HCO<sub>3</sub> =2.7 mmol/L), electrolyte imbalance (K<sup>+</sup> =2.6 mmol/L, Na =152 mmol/L, ammonia =109 μmol/L) and hyperglycemia (10.72 mmol/L). After 1 day of treatment at the local hospital, she was referred to our hospital due to exacerbated conditions including unconsciousness and convulsion. Upon admission at our hospital, she had metabolic acidosis, hypokalemia, hypernatremia, hyperammonemia, and a Glasgow coma scale of eight and Kussmaul breathing. Blood acylcarnitine analysis showed high levels of C5:1 and C5-OH at 1.22 μmol/L (ref: <0.05) and 1.42 μmol/L (ref: <0.44), respectively. Gas chromatography-mass spectrometer (GC/MS) analysis revealed a high level of 2M3HB at (43.71 mmol/mol creatinine, ref: <0.014) and TG 53.85 mmol/mol creatinine (ref: <0.001). The results revealed that the patient had a homozygous pathogenic variant of c.121-3C>G (splicing error) in the ACAT1 gene. Based on the laboratory and genetic results, the patient was diagnosed with T2 deficiency. Five percent NaHCO<sub>3</sub> (24 mL/kg), glucose and insulin (4–6 g glucose/1 U insulin) were continuously infused for correcting acidosis. L-carnitine (350 mg/kg/day) was given for ensuring the energy and increasing exudates of metabolites after admission. Protein was limited at 1.5 g/kg/day. Mechanical ventilation support and hemodialysis were used. The patient was still under the state of unconsciousness after 2 weeks of intensive treatments in our Pediatric Intensive Care Unit (PICU). Due to her severe illness, the child's

parents ultimately decided to redirect their goals of care and the child was discharged home, where she died.

This study was approved by the Ethical Committee of Children's Hospital, Zhejiang University School of Medicine (2017-IRB-034). All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient's parents.

## Discussion

T2 is important in ketogenesis both in the hepatic and extrahepatic tissues (4); in extrahepatic tissues, T2 is important in ketolysis which catalyzes predominantly acetoacetyl-CoA cleavage to form acetyl-CoA. Another thiolase, mitochondrial 3-ketoacyl-CoA thiolase, which can compensate for T2 deficiency in ketogenesis but to a lesser extent in ketolysis (2-4). Therefore, T2 deficiency leads to ketosis. In most cases with T2 deficiency, the first ketoacidotic episode is commonly very severe following conditions under ketogenic stresses, especially gastroenteritis or respiratory diseases in association with fasting and catabolic conditions (4). In T2 deficiency, catabolic conditions appear to confer a higher risk than that of protein overload. In the reports of five large series from India, Vietnam, France, Japan, Turkey, Germany and Ireland (2,3,5-7), triggers of the ketoacidotic crisis were commonly infections including gastroenteritis or respiratory infections; and only one case was triggered by excessive protein intake (*Table 1*). Literature review in the Chinese patients also revealed that infections were common triggers for ketoacidotic crisis (8-12,14); three patients in a family with two twin boys and their sister had disease onset after transition from breastfeeding to high-protein milk formula feeding (13). Our case is the first case with ketoacidotic crisis occurring after vaccination. This case in the other side reflects the importance of NBS. The appropriate precautions could be taken if the disorder was diagnosed by NBS prior to vaccination for preventing the fatal ketoacidotic crisis. We should attach importance to vaccination in the patients with inborn errors of metabolism (IEM). In general, patients with IEM are not at increased risk of metabolic decompensation following appropriate vaccinations (15,16). We should be very cautious or provide close follow-up for patients after administration of immunizations because some

**Table 1** Triggers of ketoacidotic crisis in symptomatic patients with beta-ketothiolase deficiency

Studies	Number of patients with ketoacidotic crisis	Number of patients with triggers prior to ketoacidotic crisis	Triggers or concurrent diseases
Fukao <i>et al.</i> (5)	26	14	Gastroenteritis or respiratory illness
Abdelkreem <i>et al.</i> (2)	10	8	Respiratory illness or gastroenteritis
Grünert <i>et al.</i> (6)	32	20	Gastroenteritis or respiratory infections
Paquey <i>et al.</i> (7)	26	21	Infections
Nguyen <i>et al.</i> (3)	41	39	Gastroenteritis or respiratory infections (38 cases); excessive protein intake (one cases)
Liu <i>et al.</i> (8); Shen <i>et al.</i> (9); Sun <i>et al.</i> (10); Wang <i>et al.</i> (11); Yue <i>et al.</i> (12); Wen <i>et al.</i> (13)	9	9	Gastroenteritis or respiratory infections (six cases); high-protein milk formula feeding (three cases, in one family)

inborn errors with associated impaired immune functions or tendency for rapid decompensation (17). Experts also suggest that vaccines based on live attenuated viruses should not be given to IEM (18). Particularly for the IEM patients with concurrent infection, vaccination will enhance the stress condition of the body, and induce or exacerbate the ketoacidosis episode. Our case had an undetected respiratory tract infection before vaccination; the potential infection together with vaccination may have triggered the onset of severe ketoacidotic crisis. The parents therefore filed a death lawsuit against the vaccinator and institution of vaccination. The death and the lawsuit of this case made us propose a procedure of checking temperature before vaccination for all children. Centers for Disease and Prevention of Zhejiang Province adopted the proposition, and now body temperature checking before vaccination becomes a routine procedure in Zhejiang Province.

Intensive treatment of the first acute ketoacidosis episode is imperative for better outcome; continuous infusion of intravenous glucose and electrolytes is recommended which will increase the urine volume for excretion of acids and suppress ketosis (4). Insulin can be infused together with glucose if with hyperglycemia (4). It is important to actively correct acidosis. L-carnitine is recommended to be infused at a dose of 300–500 mg/kg/day. Timely mechanical ventilation and hemodialysis can also benefit for managing acute ketoacidosis episode, however, it is a challenge for local hospitals where lacking of techniques and equipments. Most patients with T2 deficiency had favorable outcome even with severe ketoacidotic crisis. The lessons learned from our patient were as following: for children with acute

metabolic acidosis, T2 deficiency should be considered; rigorous indicative treatments including mechanical ventilation and hemodialysis should be given timely if ketoacidosis occurred in patients with T2 deficiency.

For the asymptomatic patients or those under non-episodic conditions, fasting should be avoided (13). Oral L-carnitine is recommended to be supplemented at a dose of 50–200 mg/kg/day. If patients are under ketogenic conditions, such as vomiting, appetite loss, or infections, sufficient oral glucose supplementation or glucose infusion is recommended for preventing ketoacidotic crisis (2–4). Protein intake is recommended to be restricted to 1.5–2.0 g/kg per day for patients when under stable stage from a theoretical standpoint (4). For our asymptomatic patients diagnosed by NBS, we recommend restricting protein intake to 1.5–2.0 g/kg/day for infants and 1.0–1.5 g/kg/day for those aged  $\geq 1$  year of age.

In conclusion, T2 deficiency should be considered as a differential diagnosis in patients with severe metabolic acidosis. Timely rigorous symptomatic treatment should be given to patients under ketoacidotic crisis. For patients with IEM, vaccination should be taken when under well conditions and excluding potential infections. For patients under ketogenic conditions including fasting, respiratory and gastrointestinal infections, sufficient glucose and carnitine should be supplemented for preventing ketoacidotic crisis.

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## Footnote

**Reporting Checklist:** The authors have completed the CARE reporting checklist. Available at <http://dx.doi.org/10.21037/tp-20-265>

**Conflicts of Interest:** All authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/tp-20-265>). The authors have no conflicts of interest to declare.

**Ethical Statement:** The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient's parents.

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