CASE STUDY

Diabetes ketoacidosis - a case study

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ABSTRACT

Uncontrolled hyperglycaemia can lead to diabetic ketoacidosis. It evolves within a short time and if not addressed urgently can lead to serious complications. The purpose of this case study was to interpret laboratory results and raise high risk alert and inform to physician or refer them to appropriate centres for immediate management of the condition.

Key words: diabetic ketoacidosis, Type 1 diabetes, Type 2 diabetes, glycogenesis, gluconeogenesis, glutamic acid decarboxylase antibodies, islet cell autoantibodies.

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INTRODUCTION

Diabetic ketoacidosis is a serious acute metabolic condition that is a complication of diabetes (1). It is life threatening yet preventable and results from elevated concentrations of ketone bodies and glucose in blood; a combination decreases blood pH and increases serum osmolality, which has deleterious effects on multiple body organs including the kidneys. Diabetic ketoacidosis occurs more frequently in Type 1 diabetes particularly if triggered by infection, surgery, or trauma but it can also occur in Type 2 diabetes. Timely management of this condition reduces its morbidity and mortality. We present a case of diabetic ketoacidosis in a nine-year old with previously undiagnosed Type 1 diabetes.

Background

Glucose is the primary energy source for the human body and is mostly derived from the breakdown of carbohydrates from diet. Glucose can also be synthesized endogenously from amino acids and triglycerides by the hepatocytes, by gluconeogenesis (2). Excess glucose is converted to glycogen by a process known as glycogenesis and stored in the liver and muscles. The liver glycogen stores are the main source of energy to maintain the blood glucose primarily during periods of fasting. The concentration of glucose and glycogen metabolism are regulated by multiple complex metabolic pathways. Glycogenesis is stimulated by insulin which is a hormone produced by the β-cells of the islets of Langerhans in the pancreas whereby glycogen is converted back to glucose and this process is mainly regulated by glucagon, a hormone produced by the α-cells of the pancreas (2).

Diabetes mellitus is a group of metabolic disorders of carbohydrate metabolism in which glucose is underutilized due to insulin deficiency resulting in hyperglycaemia (2). Insulin deficiency can be quantitative, as is the case in Type 1 diabetes, in which there is loss of pancreatic cells leading to low levels of insulin or no insulin due to autoimmune destruction of insulin secreting cells (2), This differs in Type 2 diabetes in which insulin concentrations may be normal or elevated but there is peripheral resistance to insulin action.

In Type 1 diabetes the islet cells are damaged by autoantibodies to insulin and glutamic acid decarboxylase (GAD). These autoantibodies are detectable years before symptoms of hyperglycaemia develop (2).

The first full description of diabetic ketoacidosis was in 1886 by Julius Dreschfeld, a German pathologist working in the United Kingdom, 35 years before insulin was discovered (3). Insulin deficiency results in a reactive increase in the activity of glucagon, cortisol, catecholamines and growth hormone in response to the inability of the body to utilise glucose (2). Figure 1 summarises pathways involved in the pathogenesis of diabetic ketoacidosis. Diabetic ketoacidosis can occur very quickly and may develop in less than 24 hours (4).

When carbohydrate metabolism is impaired, as is the case in diabetes mellitus or during prolonged starvation, stored fat becomes a source of energy (2). The “counter regulatory hormones” glucagon, cortisol, catecholamines and growth hormone trigger the breakdown of fat (lipolysis), and the release of free fatty acids from adipose tissue. Free fatty acids then are oxidised and produce large quantities of acetyl Co-A. The tricarboxylic acid cycle is a common pathway for oxidation of all food materials. In normal carbohydrate metabolism oxaloacetate produced from the tricarboxylic acid cycle gets condensed enzymatically with acetyl Co-A to produce citrate and enters the citric acid cycle, which is rate limited. In the case of diabetic ketoacidosis the excess acetyl-co-A is diverted into an alternative metabolic pathway and forms acetoacetic acid, β-hydroxybutyric acid and acetone (ketone bodies) with resultant ketonemia and metabolic acidosis. Accumulation of ketoacids increases the anion gap [anion gap= (Na^+) - $(Cl^- + HCO3^-)$], the reference range of which is +/- 12 mmol/L (1). The most important metabolic features of diabetic ketoacidosis are a high anion gap metabolic acidosis, hyperglycaemia and ketonemia (1). Peripheral high glucose leads to glycosuria, osmatic diuresis and loss of electrolytes.

Diabetic ketoacidosis is mostly observed in Type 1 diabetes patients and can be triggered by conditions of stress such as infection, myocardial infarction, stroke, anorexia or inadequate insulin administration and certain medications such as isoproterenol which is often used for treatment of bradyarrhythmia (slow irregular heart rhythm) (4,5). Diabetic ketoacidosis itself is a risk factor for stroke (6). Higher mortality rates, increased incidence of cerebral odema, sepsis, shock and renal failure have been identified in children with diabetic ketoacidosis from developing countries (7). A root cause for such complications and for increased mortality in diabetic ketoacidosis could be delayed diagnosis in children, which is common in these regions (7). Prior to the discovery of insulin, diabetic ketoacidosis was associated with a very high mortality rate. Due to awareness and eventual availability of synthetic insulin, the rate of diabetic ketoacidosis associated mortality is reduced and the incidence of diabetic ketoacidosis associated serious conditions, such as cerebral odema and renal failure, have decreased significantly (0.15%-0.31%) in developed countries (7).

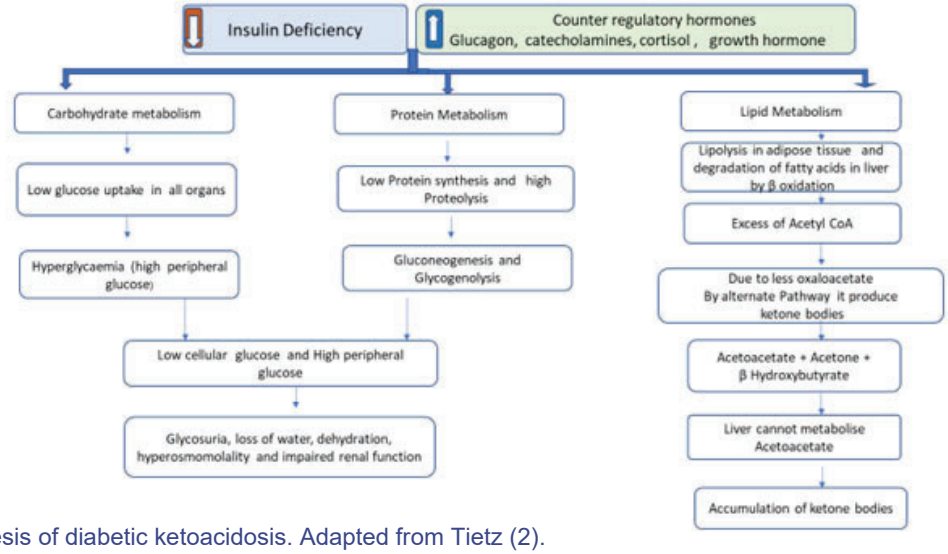

Figure 1. Pathogenesis of diabetic ketoacidosis. Adapted from Tietz (2).

CASE

A nine-year old boy presented to his general practitioner (GP) in the morning with a week-long history of extreme lethargy, polydipsia, and polyuria, particularly at night. The mother had noticed recent weight loss and faster breathing. He had a history of a leg injury one year prior but otherwise no recent illness. On examination he had dry mucous membranes, reduced skin turgor, and Kussmaul breathing (rapid deep breathing with a fruity smell, also called acidotic breathing). There was no known family history of Type 1 diabetes. The GP requested laboratory investigations which are summarised in Table 1.

In the laboratory blood glucose was measured on a Roche COBAS platform by the hexokinase enzyme method. Bicarbonate was a reflex test added because of the elevated glucose as per the laboratory's protocol. It was measured on a Siemen's Advia 2400 platform utilising phosphoenolpyruvate carboxylase and malate dehydrogenase catalysed reactions. Creatinine and electrolytes were also measured on the Siemens Advia 2400 platform. Creatinine was measures by the kinetic Jaffe methodology with rate blanking and intercept correction. (Package insert, Advia Chemistry XPT)

Table 1. Laboratory results.

Analyte	Reference range (Laboratory 1)	Day 1 Lab 1	Day 1 Lab 2	Day 2 Lab 3	Day 6 Lab 3
Sodium mmol/L	135-145	137	137		
Potassium mmol/L	3.5-5.2	4.2	4.5		
Creatinine umol/L	<65	99	115	58	
Bicarbonate umol/L	22-31	12			
Glucose mmol/L	3.5-7.7	32.2	41.9		
β-hydroxy butyrate mmol/L	0.0-0.27		10.3	3.6	
Urea mmol/L	3.2-7.7		6.8	5.2	
Albumin g/L	32-48		46	35	29
Protein g/L	66-84		90		
Globulin g/L	25-41		44		
Bilirubin umol/L	<25		3	4	
GGT U/L	0-60		12		
ALP U/L	80-450		370	261	
ALT U/L	<45		20	10	
Phosphate mmol/L	1.00-1.85			0.35	1.06
Calcium mmol/L	2.1-2.55				2.29
Blood pH	7.30-7.40		6.9		
Haemoglobin g/L	115-145		135		
Red cell count 12e9/L	4.20-5.60		4.96		
Platelets 10e9/L	150--425		439		
White cell count 10e9/L	4.30-12.00		21.40		
Neutrophils 10e9/L	1.5- 7.00		16.95		
HbA1c mmol/mol	<41		111		
Total cholesterol mmol/L	< 5.0		6.3		
Triglycerides mmol/L	<2.0		4.8		
High density lipoprotein mmol/L	>1.0		0.87		
Glutamic Acid Decarboxylase Autoantibodies(GAD) GAD IgG IU/mL	<10				447
Islet cell autoantibodies (IA-2 IgG) IU/mL	<10				>4000

Based on the results and clinical presentation diabetic ketoacidosis was suspected and the patient was referred to hospital. On admission he was alert, had Kussmaul breathing, blood pressure was stable, had dry mucous membranes and reduced skin turgor, chest was clear and abdominal examination showed no organomegaly (enlarged organs such as the liver). Weighing confirmed a 5 Kg weight loss (according to the mother). Further tests were carried out in the hospital which showed a rising glucose and creatinine, elevated β-hydroxybutyrate and low pH and high HbA1c (Table 1).

DISCUSSION

Classic clinical symptoms of diabetic ketoacidosis include polyuria and dehydration, weight loss contributed to by fluid loss, vomiting, abdominal pain, weakness and change in mental status (1). Typical physical signs include loss of skin turgor due to dehydration, Kussmaul breathing due to acidosis, tachycardia, and less commonly seizures (1). Our patient had most of these symptoms and signs.

Diabetic ketoacidosis can be classified as mild, moderate or severe based on the concentration of blood bicarbonate and on mental status (1). A bicarbonate between 15 and 18 mmol/L is classified as mild diabetic ketoacidosis; <15 mmol/L as moderate diabetic ketoacidosis; and <10 mmol/L as severe diabetic ketoacidosis. Our patient had a bicarbonate of less than 12 umol/L which suggested moderate to severe diabetic ketoacidosis (1). Studies show that serum osmolarity and mental alertness correlate (1). Calculated osmolarity in this case in hospital (laboratory 2) was >320 mOsm/kg (reference range: 280-300 mOsm/kg).

Creatinine was elevated in the first day but had decreased by the next day (Table 1). Dehydration was probably the main reason for this with the creatinine normalising after in-hospital rehydration and management. Ketone bodies and high glucose levels are known to falsely elevate creatinine measured by some Jaffe methods (2). However, the manufacturer's package insert makes no reference to interference by glucose or ketone bodies.

Insulin promotes the movement of potassium into cells, therefore in the absence or deficiency of insulin potassium concentrations in the plasma may be within the reference range or elevated in spite of tissue deficiency. However, administration of insulin would facilitate the transfer of potassium back into the cells and may promote hypokalaemia if not done with caution and regular monitoring. In our patient's case potassium was found to be normal when presented to the community laboratory and remained stable after admission. Insulin also promotes the intracellular movement of phosphate and it may have contributed to the low level of phosphate (0.35 mmol/L) on the third day. Our patient also had elevated triglycerides and low high density lipoprotein cholesterol. These findings are consistent with the derangement in lipid metabolism in diabetes mellitus.

Glycated haemoglobin (HbA1c) is formed by condensation of glucose with the N-terminal valine residue of each β-chain of haemoglobin to from a stable compound known as HbA1c. The amount of HbA1c depends on the life span of red blood cells that is an average 120 days. The rate of formation of HbA1c is directly proportional to glucose in the blood and thus HbA1c is a marker of blood glucose in last 120 days (2). In our patient HbA1c was significantly elevated, which indicated longstanding hyperglycaemia.

Our patient had elevated white blood cell, neutrophil and platelet counts (Table 1). These findings cannot exclude the existence of an infection that may have worsened his already deranged glucose metabolism and precipitated diabetic ketoacidosis. On the other hand, diabetic ketoacidosis can in itself increase white cell count (4).

Laboratory results confirmed the presence of glutamic acid decarboxylase antibodies and islet cell autoantibodies which indicates that the patient has Type 1 diabetes. These autoantibodies are associated with the development of Type 1 diabetes.

In New Zealand approximately 4,263 new cases of diabetes (Type 1 and Type 2 diabetes inclusive) were registered in 2017 (8). In the same year, data published by the Australian Institute of Health and Welfare revealed that 9% of diabetics were diagnosed with Type 1 diabetes in Australia (9). Data from three registries and audits from five countries (Austria, Germany, England, Wales, and the Unites States) was analysed for 49,859 individuals less than 18 years old with Type 1 diabetes (10). The rates of diabetic ketoacidosis ranged from 5% to 7.1% (10).

The incidence of diabetic ketoacidosis is higher in developing countries compared to developed countries (7). Admission for diabetic ketoacidosis was 10 times higher for young diabetics (0 - 24 years old) compared to other age groups in developing countries, due to factors like delayed diagnosis of diabetes mellitus and of diabetic ketoacidosis (7). Reasons for a delayed diagnosis of diabetic ketoacidosis include a lack of parental awareness about diabetic symptoms, lack of awareness among physicians, mis-interpretation of diabetic symptoms, lack of finger prick estimation of blood glucose in known diabetics, not recognizing laboratory abnormalities consistent with diabetic ketoacidosis, lack of immediate referral, delay in transport to an appropriate centre or emergency department and delayed referral for specialist care (7). Knowledge and awareness can reduce the incidence of diabetic ketoacidosis and its complications. An example of a successful awareness program exists in Italy. Simple awareness programs in Italian schools and physicians' offices over a five-year period, in the form of posters depicting signs of diabetes, have helped to significantly reduce the occurrence of diabetic ketoacidosis there (7).

Our patient is thriving and put on 7 Kg within a few weeks of management. He has learnt to self-administer insulin and his HbA1c dropped to 55 mmol/mol after 3 months. His growth is within the 95th to 98th percentile range.

Take home messages

- The diagnosis of diabetic ketoacidosis can easily be missed in children due to lack of awareness
- Diabetic ketoacidosis should be considered as a potential cause when a child presents with abdominal pain, a relatively common and potentially vague symptom
- It is prudent on laboratories to implement reflex testing of bicarbonate if blood glucose levels are above a pre-set threshold, particularly in children, to support timely detection of metabolic acidosis and diabetic ketoacidosis.
- It is worthwhile including as much clinical information on request forms to guide scientists and pathologists to interpret critically abnormal results.

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