CASE REPORT

Lactation ketoacidosis: case presentation and literature review

Abdullah M Al Alawi,^{1,2} Henrik Falhammar^{3,4}¹Royal Darwin Hospital, Casuarina, Australian Capital Territory, Australia²Department of Medicine, Sultan Qaboos University, A'Seeb, Muscat, Oman³Department of Endocrinology, Metabolism and Diabetes, Karolinska University Hospital, Stockholm, Sweden⁴Department of Molecular Medicine and Surgery, Karolinska Institutet, Stockholm, Sweden

Correspondence to

Dr Abdullah M Al Alawi,
dr.abdullahalawi@gmail.com

Accepted 28 February 2018

SUMMARY

A 35-year-old woman presented to the emergency department with a 2 days history of malaise and headache. She was breastfeeding her 5-month old infant and had recently started an altered diet based on reducing carbohydrate amount. Moreover, she had also started exercising 2 weeks prior to her illness. Initial blood tests revealed high anion gap metabolic acidosis and hypoglycaemia (pH 7.13 (normal 7.30–7.40), bicarbonate 9.4 mmol/L (normal 21.0–28.0), anion gap 22.6 mmol/L (normal 8–12), glucose 2.9 mmol/L (normal fasting 3.9–5.8) and ketones 6.4 mmol/L (normal <0.6)). The patient was treated with intravenous dextrose and showed complete resolution of ketoacidosis and hypoglycaemia within 48 hours. She was discharged home and remained well with a balanced diet. After excluding all other the causes of hypoglycaemia and ketoacidosis, the diagnosis of lactation ketoacidosis was made and it was considered triggered by altered diet, exercise and skipping meals. All 11 cases of lactation ketoacidosis which has previously been published are reviewed as well.

BACKGROUND

Metabolic acidosis can be classified according to anion gap. Causes of raised anion gap metabolic acidosis include: ketoacidosis, lactic acidosis and ingestion of toxins such as aspirin, methanol and ethylene glycol.¹ In addition, some types of inborn error of metabolism can cause high anion gap metabolic acidosis but usually present in infancy or early childhood.²

Diabetic ketoacidosis is the most common cause of ketoacidosis. Mild degree of ketosis can occur after 12–14 hours of fasting but significant starvation ketoacidosis may require more than 20 days of continuous fasting.^{3–4} Lactation ketoacidosis or 'bovine ketoacidosis' is a well-described condition in cows which occurs in early lactation when high demand of glucose creates negative energy balance that leads to fat mobilisation, ketosis and ketoacidosis.⁵ Lactation ketoacidosis is a rare phenomenon in humans with the first case reported in 1982.⁶ We present the first case of lactation ketoacidosis with hypoglycaemia on presentation.

CASE PRESENTATION

A 35-year-old lactating woman, 23 weeks post partum, presented to the emergency department (ED) with headache and severe malaise of 2 days duration. She was trying to lose weight by

reducing carbohydrate intake and had commenced exercising 2 weeks earlier (60 min daily running 6 days a week). In addition, she regularly missed her lunch meal due to her busy life. Her weight was normally 67 kg but she had lost around 6 kg in 2 weeks. No history of recent infection, fever, chills, abdominal pain, nausea, vomiting or diarrhoea was noted. Moreover, no history of alcohol, methanol, ethylene glycol, aspirin or recreational drug intake was reported either. Her last pregnancy had been uncomplicated. She had a normal vaginal delivery at week 40 and had been well. Since previously she had two sons aged 3 and 5 with uneventful pregnancies and postnatal periods. As a child, she had been treated for epilepsy but there had been no seizure since the age of 12 and her antiepileptic medications had been ceased when she was 25 years old. Otherwise she had been healthy and was not on any regular medication. There was no family history of metabolic or endocrine disorder.

On presentation to the ED, she looked very unwell and drowsy. Her vital signs were stable (temperature 37.0°C, blood pressure 140/70, heart rate 93 bpm and regular, oxygen saturation 100% on room air). Systemic examination was unremarkable.

INVESTIGATIONS

A venous blood gas revealed: pH 7.13 (normal 7.30–7.40), bicarbonate 9.4 mmol/L (normal 21.0–28.0), base excess –18.5 mmol/L (normal –2–2), haemoglobin 143 g/L, sodium 138 mmol/L (normal 135–145), potassium 5.45 mmol/L (normal 3.5–4.5), anion gap 22.6 mmol/L (normal 8–12), measured osmolality 279.7 mmol/kg (normal 275–295), calculated osmolality 281 mmol/kg (normal 275–295), glucose 2.9 mmol/L (normal fasting 3.9–5.8), lactate 0.7 mmol/L (normal 1.5–2.5), creatinine 72 µmol/L (normal 50–100), urea 2.4 mmol/L (normal 2.5–7.0) and beta-hydroxybutyrate 6.4 mmol/L (normal <0.6). Other investigations including ECG, chest X-ray, CT brain, plasma/serum insulin, C-peptide, thyroid function tests in addition to urine test screen for amino and organic acids were unremarkable. A morning serum cortisol was 585 nmol/L (normal 101–536) which was considered normal.

DIFFERENTIAL DIAGNOSIS

Treatment

She was given 25 mL of 50% dextrose intravenously followed by 4000 mL of 10% dextrose infusion over 48 hours. The infant could not tolerate

To cite: Al Alawi AM, Falhammar H. *BMJ Case Rep* Published Online First: [please include Day Month Year]. doi:10.1136/bcr-2017-223494

Figure 1 Time of resolution of ketoacidosis.

milk formula, so the patient opted to continue breastfeeding. Following treatment, she showed complete resolution of her symptoms and the ketoacidosis disappeared within 48 hours (figure 1). The patient was discharged home with advice to have a balanced diet and to avoid missing meals.

OUTCOME AND FOLLOW-UP

She was reviewed in outpatient clinic 2 and 6 weeks later and remained asymptomatic with normal biochemical tests. A

diagnosis of lactation ketoacidosis was made since other possibilities had been excluded.

DISCUSSION

During times of carbohydrate deficiency, human body produces ketone bodies (acetoacetate, 3-hydroxybutyrate and acetone) to spare glucose use and minimise protein breakdown.⁷ The process of ketogenesis is regulated by insulin which has an inhibitory role and by epinephrine and glucagon which stimulate ketogenesis.⁸

Table 1 Review of reported cases of lactation ketoacidosis

First author, year	Country	Age of mother (years)	Age of child (weeks)	pH	P-glucose (mmol/L)	Ketones	Precipitating factors
Chernow 1982 ⁶ (3)	USA	19	30.4	7.25	11	Urine ketones +	Weight reduction diet
Altus 1983 ¹¹ (9)	USA	30	14	7.07	4.2	Urine ketones +	High protein, low carbohydrate diet
Heffner 2008 ¹² (10)	USA	35	12	7.24	3.8	Serum ketones +	Altered diet
Sandhu 2009 ¹³ (11)	USA	36	5	6.9	7.4	Urine ketones +	High-protein carbohydrate-free meals
Szulewski 2012 ⁹ (6)	Canada	35	3	7.15	6.3	Serum ketones +	Preoperative prolonged fasting
Von Geijer 2015 ¹⁶ (14)	Sweden	32	43.5	7.2	3.8	Serum ketones +	Low carbohydrate, high-fat diet
Wuopio 2015 ¹⁵ (13)	Sweden	21	6	6.92	4.4	Serum ketones +	Low carbohydrate diet
Hudak 2015 ¹⁴ (12)	Germany	32	3	6.99	3.8	Urine ketones +	Reduced oral intake, nausea and vomiting
Greaney 2016 ¹⁷ (15)	Ireland	36	9	6.88	5.7	Serum ketones +	High protein and low carbohydrate Skipped meals
Gleeson 2016 ² (8)	New Zealand	31	43.5	7.26	3.8	Serum ketones +	None identified
Sloan 2017 ⁸ (5)	UK	27	8	7.02	3.6	Serum ketones +	Low carbohydrate diet
Al Alawi (2018)	Australia	35	21.7	7.13	2.9	Serum ketones +	Altered diet, skipping meals and exercise
Median (IQR)	—	32 (IQR=6.5)	10.5 (IQR=23)	7.1 (0.27)	4.0 (IQR=2.2)	—	—

Excessive ketogenesis can lead to high hydrogen load and hence high anion gap metabolic acidosis. This is commonly seen in diabetic ketoacidosis but less commonly observed in starvation and alcoholic ketoacidosis.⁹

Lactation ketoacidosis was originally described in cattle where lactating cows developed severe ketosis.^{5 10} This occurred because they relied completely on hepatic gluconeogenesis for their glucose supply needed for milk production. In humans, lactation ketoacidosis is a very rare phenomenon and until there are only 11 cases reported in literature (table 1).^{2 6 8 9 11–17}

Patients in these studies presented with non-specific symptoms including headache, malaise, lethargy, nausea, vomiting, abdominal pain and dyspnoea. Similar to our patient, weight loss was reported in some of the previously reported cases.^{6 11 13 16} Reduced carbohydrate or calorie intake diet was the most common identified precipitating factor. Other causes included intercurrent illness and fasting. Almost all patients were euglycaemic on presentation with high anion gap metabolic acidosis. Intravenous dextrose therapy was the main treatment that led to a rapid resolution of acidosis. Insulin and bicarbonate have been used as additional treatments in a minority of patients probably unnecessary. The majority of patients were able to resume breastfeeding. Treating the underlying cause and having a balanced diet were associated with good outcomes. To date, there is no reported mortality because of lactation ketoacidosis. Majority of women in the cited studies were in their late 20s to mid-30s, and most infants were less than 3 months of age.

Our patient had no history of ingestion of ethanol, methanol, ethylene glycol or salicylate which can present with high anion gap metabolic acidosis. In addition, we considered the possibility of a late presentation of an inborn error of metabolism disorder, such as defects of fructose-1,6-bisphosphatase and medium-chain acyl-CoA dehydrogenase deficiency, as a cause of high anion gap metabolic acidosis and hypoglycaemia.^{18 19} However, ketosis is not a presenting feature of these disorders and urine screen did not detect any amino or organic acids.

Our case is the first reported case of lactation ketoacidosis with hypoglycaemia on presentation. We believe that skipping meals, reduced carbohydrate intake and starting aerobic exercise

were precipitating factors for our patient. Her main symptoms were malaise and severe frontal headache which resolved with intravenous dextrose infusion. Intravenous dextrose was ceased after 48 hours and patient was discharged from the hospital with an advice to have a balanced diet and to avoid skipping meals. She had two other children and she had breastfed both of them without any issue indicating that lactation ketoacidosis might be a conditional problem related to the nutritional status rather than a problem related to genetic predisposition or enzyme deficiency as in the case of an inborn error of metabolism disorder.

Contributors AMAA: gathered clinical information, did part of literature review and wrote the first draft of the case report including creating table and figure. HF: helped with literature review, reviewed manuscript and provided expert opinion regarding inclusion of appropriate differentials and investigations. He reviewed the manuscript and added comments and suggestions.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

© BMJ Publishing Group Ltd (unless otherwise stated in the text of the article) 2018. All rights reserved. No commercial use is permitted unless otherwise expressly granted.

REFERENCES

- Gabow PA. Disorders associated with an altered anion gap. *Kidney Int* 1985;27:472–83.
- Gleeson S, Mulroy E, Clarke DE. Lactation ketoacidosis: an unusual entity and a review of the literature. *Perm J* 2016;20:71–3.
- Reichard GA, Owen OE, Haff AC, et al. Ketone-body production and oxidation in fasting obese humans. *J Clin Invest* 1974;53:508–15.
- Cahill GF. Fuel metabolism in starvation. *Annu Rev Nutr* 2006;26:1–22.
- Vasilev B. [Blood sugar and ketone body content in cows with clinical ketosis]. *Vet Med Nauki* 1977;14:95–103.
- Chernow B, Finton C, Rainey TG, et al. "Bovine ketosis" in a nondiabetic postpartum woman. *Diabetes Care* 1982;5:47–9.
- Laffel L. Ketone bodies: a review of physiology, pathophysiology and application of monitoring to diabetes. *Diabetes Metab Res Rev* 1999;15:412–26.
- Sloan G, Ali A, Webster J. A rare cause of metabolic acidosis: ketoacidosis in a non-diabetic lactating woman. *Endocrinol Diabetes Metab Case Rep* 2017;2017.
- Szulewski A, Howes D, Morton AR. A severe case of iatrogenic lactation ketoacidosis. *BMJ Case Rep* 2012;2012:bcr1220115409.
- Bell AW, Bauman DE. Adaptations of glucose metabolism during pregnancy and lactation. *J Mammary Gland Biol Neoplasia* 1997;2:265–78.
- Altus P, Hickman JW. Severe spontaneous 'bovine' ketoacidosis in a lactating woman. *J Indiana State Med Assoc* 1983;76:392–3.
- Heffner AC, Johnson DP. A case of lactation "bovine" ketoacidosis. *J Emerg Med* 2008;35:385–7.
- Sandhu HS, Michels MF, DeVita MV. A case of bovine ketoacidosis in a lactating woman. *NDT Plus* 2009;2:278–9.
- Hudak SK, Overkamp D, Wagner R, et al. Ketoacidosis in a non-diabetic woman who was fasting during lactation. *Nutr J* 2015;14:117.
- Wuopio J, Schiborr R, Charalampakis G. [Severe ketoacidosis in breastfeeding woman with low energy and carbohydrate intake]. *Lakartidningen* 2015;112.
- von Geijer L, Ekelund M. Ketoacidosis associated with low-carbohydrate diet in a non-diabetic lactating woman: a case report. *J Med Case Rep* 2015;9:224.
- Greaney DJ, Benson P. Life-threatening lactation or "bovine" ketoacidosis: a case report. *AA Case Rep* 2016;7:81–4.
- Krishnamurthy V, Eschrich K, Boney A, et al. Three successful pregnancies through dietary management of fructose-1,6-bisphosphatase deficiency. *J Inher Metab Dis* 2007;30:819.
- Feillet F, Steinmann G, Vianey-Saban C, et al. Adult presentation of MCAD deficiency revealed by coma and severe arrhythmias. *Intensive Care Med* 2003;29:1594–7.

Learning points

- ▶ Lactation ketoacidosis is a rare condition and should be diagnosed after excluding other causes of raised anion gap metabolic acidosis.
- ▶ Lactating women may present with non-specific symptoms and a negative energy balance due to diet, exercise, skipping meals or fasting.
- ▶ Intravenous dextrose infusion is the treatment of choice and is associated with good and rapid recovery.
- ▶ Majority of patients reported in previous case studies and in our case were able to resume breastfeeding.
- ▶ With a balanced diet and treatment of underlying condition, this condition is unlikely to reoccur and there is no reported mortality in literature up to date.

Copyright 2018 BMJ Publishing Group. All rights reserved. For permission to reuse any of this content visit <http://group.bmj.com/group/rights-licensing/permissions>.
BMJ Case Report Fellows may re-use this article for personal use and teaching without any further permission.

Become a Fellow of BMJ Case Reports today and you can:

- ▶ Submit as many cases as you like
- ▶ Enjoy fast sympathetic peer review and rapid publication of accepted articles
- ▶ Access all the published articles
- ▶ Re-use any of the published material for personal use and teaching without further permission

For information on Institutional Fellowships contact consortiasales@bmjgroup.com

Visit casereports.bmj.com for more articles like this and to become a Fellow