An unusual case of severe high anion gap metabolic acidosis

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Abstract
We present a case of high anion gap metabolic acidosis with an unusual aetiology in a 75-year-old lady with hypoglycaemia, encephalopathy and relatively preserved renal function. Full toxicology and biochemical analysis suggested that she had an inborn error of metabolism, riboflavin-responsive multiple acyl-CoA dehydrogenase deficiency that can predispose to severe acidosis in situations where caloric intake is reduced. We believe this to be one of the few published cases and is remarkable for the presentation in late adulthood in addition to the requirement for emergency haemodialysis due to the severity of the metabolic disturbance.

Keywords: acyl carnitine; fatty acid metabolism; metabolic acidosis; riboflavin-responsive multiple acyl-CoA dehydrogenase deficiency

Case report

A 75-year-old woman presented with a 9-day history of general malaise, anorexia and vomiting. She had consumed only lemonade and occasional soft diet for several weeks and became drowsy 24 h prior to admission. Her background medical history included schizophrenia and depression.

She had been admitted to hospital 2 years previously with similar symptoms but had seizure activity as well as extreme metabolic acidosis requiring dialysis. Toxicology screening did not suggest common overdoses as a likely cause. At that time, she was extremely cachectic and a diagnosis of starvation ketoacidosis was made on the basis of exclusion and high serum levels of acetone.

On her current admission, she was drowsy with a Glasgow Coma Scale of 9/15. Other observations included a heart rate of 120 beats/min and blood pressure of 140/70 mmHg. Her respiratory rate was 26/min. Systemic examination was otherwise unremarkable.

Finger prick testing showed capillary blood glucose of 1.8 mmol/L (3.5–5.5 mmol/L) and urine dip was positive for ketones. Her blood gas analysis on admission revealed that she had severe metabolic acidosis with a high anion gap. She had a pH of 7.01 (7.35–7.45), pCO2 1.9 kPa (4.5–6) or 14.2 mmHg (35–45), bicarbonate 5 mmol/L (22–28), lactate 0.5 mmol/L (0.5–1.6), base excess −25.5 (−2 to +2) and pO2 13.8 kPa (10.5–13.5) or 103.5 mmHg (80–100). Her anion gap (AG) was 25.5. The low level of pCO2 reflects respiratory compensation, which is appropriate in this patient (−1.2 mmHg decrease in pCO2 for every 1 mmol/L decrease in HCO3).

Her blood tests showed sodium of 137 mmol/L, potassium 5.9 mmol/L, urea 11.5 mmol/L (2.5–7.5) and creatinine 126 μmol/L (60–110). Her measured serum osmolality was 331 mOsm/kg (278–305) as compared to a calculated osmolality of 287 mOsm/kg (osmolar gap 44 mOsm/kg). There was no improvement in her biochemistry or acidosis with initial fluid resuscitation, and her urine output was poor and on repeated testing, her serum potassium had risen to 7 mmol/L. In the presence of an elevated osmolar gap and anion gap, the differential diagnosis included salicylate, methanol and ethylene glycol poisoning. Relevant toxicology screens were sent and she was commenced on intravenous ethanol in view of the possibility of ethylene glycol poisoning, which was later converted to Fomepizole [1]. She was referred to the renal team and emergency haemodialysis was initiated. Following dialysis, her repeat arterial blood gases were much improved with a pH of 7.43, HCO3 21.2 mmol/L, base excess −4.8 and AG 16.

Serum toxicology screen was negative for paracetamol, salicylates, ethanol and methanol. However, ethylene glycol (antifreeze) was initially reported to be detectable at 238 mg/L. Despite extensive questioning, the patient and her close family members denied that the patient had ingested any substance that could potentially contain ethylene glycol. Subsequent retesting of the initial sample revealed that ethylene glycol in fact was not present; the false-positive result was due to interference with the assay by the gel in SST blood sampling tubes [2]. Her initial urine sample did not demonstrate oxalate crystals.

In view of the unexplained elevated anion gap acidosis, further investigations on patient’s admission blood and urine samples were performed. Urine analysis demonstrated high levels of beta-hydroxybutyrate and glutarate with no glycolate or oxalate. Therefore, the patient displayed significant ketoacidosis with hypoglycaemia in the absence of alcohol excess. On this admission, the patient was no
Fig. 1. The initial step in fatty acid (FA) metabolism is the transfer of FA into the mitochondria for beta oxidation. This requires the help of several mitochondrial enzymes that includes acyl-CoA dehydrogenase and carnitine acyltransferases. r-MADD is caused by defective transfer of electrons from primary flavoprotein dehydrogenases to the mitochondrial respiratory chain. Defective ETF, ETF-QO genes combined with effects of starvation leads to carnitine deficiency which causes accumulation of fatty acylCoA, fatty acylcarnitine. Carnitine acts as a buffer for excessive accumulation of intra-mitochondrial acyl CoAs.

Table 1. Acyl carnitine profiles at presentation and with riboflavin and carnitine supplementation

| Urine Organic Acids | At presentation | After 10 days (treatment not commenced) | With riboflavin supplementation alone | After riboflavin and carnitine supplementation |
|---------------------|----------------|----------------------------------------|--------------------------------------|---------------------------------------------|
| Ketonuria with a disproportionately elevated dicarboxylic and 3(OH) dicarboxylic aciduria (grossly increased adipate, increased 3-hydroxydecanedioate and octenedioate). Increased glutarate excretion | Moderate increased excretion of adipate which may be significant or may be secondary to a resolving ketosis—however, no ketones were present in this urine. | No significant abnormality | No significant abnormality |
| Plasma carnitine profile (free carnitine, acylcarnitine profile) | Low free carnitine 12 (15–53 μmol/L), elevated acylcarnitines, C4—1.17 μmol/L (ref < 0.4), C5—1.5 μmol/L (ref < 0.5), C5-DC/C10 OH—0.20 μmol/L (ref < 0.06) | Low free carnitine 7.8 (15–53 μmol/L), elevated acylcarnitines, C8—0.24 μmol/L (ref < 0.22), C10—0.50 μmol/L (ref < 0.3) | Low free carnitine 3.6 (15–53 μmol/L), elevated acylcarnitines, C8 is 0.46 (ref < 0.22), C10 is 0.85 (ref < 0.3), C12 is 0.15 (ref < 0.1), C14: 1 is 0.20 (ref < 0.18), C18: 1 is 0.29 (ref < 0.28) |

Both the initial profile plus the disappearance of urinary glutarate and the normalization of plasma acyl carnitines with treatment support the diagnosis of r-MADD. Elevated hydroxybutyrylcarnitine and generalized increase of medium to long chain acylcarnitines are both indicative of lipolytic and ketogenic response to metabolic stress.
longer cachectic and had gained 3 kg in weight as compared to previously. A plasma acylcarnitine profile showed that the levels of glutarate, parahydroxylactate, hydroxycarboxilic acid and acetone levels were elevated. These results were consistent with a lipolytic and ketogenic response to metabolic stress; other features of the plasma and urinary profile were consistent with mild riboflavin-responsive multiple acyl-CoA dehydrogenase deficiency (rr-MADD), see Table 1.

The patient was commenced on riboflavin 150 mg once daily (on Day 10) and was later prescribed carnitine supplementation. She was subsequently discharged home having made a full recovery.

**Diagnosis**

rr-MADD can be diagnosed by assessing the clinical and biochemical response to a challenge with riboflavin and also by dermal fibroblastic DNA analysis. In this case, the commencement of riboflavin supplementation has resulted in a significant clinical improvement with no further vomiting, drowsiness or encephalopathy and a subjective improvement of activity levels, which has been maintained after 9 months of follow-up. As the biochemical abnormalities sometimes persist despite riboflavin supplementation, a clinical response to treatment is often taken as the more important indicator when evaluating a patient with suspected rr-MADD. However, in this patient, the biochemical improvement with riboflavin and carnitine supplementation is also strongly supportive of the diagnosis (Table 1). Unfortunately, the patient has declined a skin biopsy required for definitive genetic diagnosis.

**Discussion**

Fatty acid metabolism is an important step in providing energy for cardiac and skeletal muscle. Multiple acyl-CoA dehydrogenase deficiency (MADD) is a disorder of oxidative metabolism involving enzymes in the oxidation pathway of fatty acids. The underlying biochemical abnormality is an impairment of dehydrogenation reactions due to defective transfer of electrons from primary flavoprotein dehydrogenases to the mitochondrial respiratory chain (electron transfer flavoproteins (ETF) Figure 1). It is now understood that there are multiple underlying genetic defects that may result in MADD with mutations in ETF-A, ETF-B or ETF-DH genes having been described [3–5]. When one of these enzymes is defective or missing the pathogenic accumulation of breakdown products in cells causes the signs and symptoms of MADD: metabolic acidosis, a musty smell in the breath, hypoglycaemia and deranged liver function tests. During relatively short periods of starvation or increased physical exercise, these patients can quickly develop hypoglycaemia with associated ketoacidosis. The treatment for rr-MADD is riboflavin supplementation (the cofactor for ETF and ETF-QO) [6–8] and starvation avoidance.

Mutations that cause a complete loss of the ETF-A, ETF-B or ETF-D-H genes result in the most severe symptoms of MADD, associated with premature birth and early death, both with and without congenital abnormalities. Mutations that allow the enzyme products to retain some activity result in milder forms of the disorder (rr-MADD) with a delayed presentation in early adulthood. Our patient was significantly older than the vast majority of patients in which this condition has previously been reported [9]. As such, this resulted in significant diagnostic difficulty and for this reason is worthy of note. We also believe this to be the first reported case in which the affected individual required emergency dialysis for the severity of the metabolic disturbance.

Conflict of interest statement. None declared

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