CASE REPORT

Medium-chain acyl-Coenzyme A dehydrogenase deficiency (MCADD): a cause of severe hypoglycaemia in an apparently well child

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SUMMARY

Medium-chain acyl-Coenzyme A dehydrogenase deficiency (MCADD) is a disorder of fatty acid β oxidation inherited in an autosomal recessive manner. The enzyme is useful in hepatic ketogenesis, a major source of energy once hepatic glycogen stores become depleted during prolonged fasting. It is a cause of hypoketotic hypoglycaemia in a previously well child. MCADD is not part of newborn screening in Ireland; children are likely to be missed if routine hypoglycaemic screen is not instituted when blood glucose level is below 2.6 mmol/L. This is a case of an otherwise healthy 23-month-old baby girl who presented with severe hypoglycaemia with some initial diagnostic dilemma.

BACKGROUND

Medium-chain acyl-Coenzyme A dehydrogenase (MCAD) deficiency (MCADD) is a disorder of fatty acid β oxidation inherited in an autosomal recessive manner. The enzyme is useful in hepatic ketogenesis, a major source of energy once hepatic glycogen stores become depleted during prolonged fasting. It is a cause of hypoketotic hypoglycaemia in a previously well child. MCADD is not part of newborn screening in Ireland; children are likely to be missed if routine hypoglycaemia screening is not instituted when the blood glucose level is below 2.6 mmol/L. This is a case of an otherwise healthy 23-month-old baby girl who presented with severe hypoglycaemia with some initial diagnostic dilemma.

CASE PRESENTATION

A 23-month-old baby girl brought into resuscitation by an ambulance with a 24-hour history of being unwell, 18-hour history of persistent vomiting and progressively worsening lethargy. There was no history of diarrhoea or fever. There were no contacts with the sick. She had been an otherwise well child with no developmental concerns, and no known family history of metabolic disorder or sudden infant death syndrome.

On examination, she was very lethargic and peripherally shut down evidenced by marked cold extremities and hypothermia. Urgent capillary blood glucose was 1 mmol/L. Systemic examination revealed no significant finding besides being hyperaemic and non-exudative pharynx.

She was actively resuscitated. Blood glucose level minimally increased to 1.3 mmol/L following

glucogel therapy before ultrasound-guided cannulation was achieved. Blood samples were taken for hypoglycaemia screening and partial septic screening including renal, liver and bone profile. Urine dipstick test performed in the emergency room showed ketones and traces of protein. Subsequently she received two boluses of 2 mL/kg of 10% dextrose solution and was maintained on dextrose saline solution.

Over the next several days, she stabilised although there was a documented hypoglycaemia (2.8 mmol/L) while on intravenous fluids. Initial half hourly glucose checks were reduced to hourly checks. Her blood sugar level was in the range of 3.8–4.8 mmol/L while on intravenous fluids and oral feeds.

She spent a total of 6 days on the ward before she was transferred to the metabolic unit.

INVESTIGATIONS

Venous blood gas on presentation revealed metabolic acidosis (pH 7.28, partial pressure of carbon dioxide (pCO₂) 5.3, partial pressure of oxygen (pO₂) 5.8, bicarbonate 18, base excess 7.9, lactate 5) which was normal repeat postresuscitation (pH 7.42, pCO₂ 4.4, pO₂ 8.6, bicarbonate 21.4, lactate 2.3). Cortisol level (4354; significant adrenal response), C peptide (173), insulin (20), growth hormone (1.95), insulin-like growth factor 1 (57) and electrolytes were within normal limits with raised urea level (12.6). Basic blood tests showed C reactive protein of 26.4, alanine transaminase of 85, total white cell count of 27.5 with absolute neutrophilia (23.2). Blood culture, urine culture and chest radiograph were unremarkable.

Acyl carnitine profile revealed free carnitine (40 (15.5–46.7)), hexanoylcarnitine (1.02 (0–0.15)), octanoylcarnitine (7.8 (0–0.27)), decanoylcarnitine (1.22 (0–0.25)), decanoylcarnitine (0.67 (0–0.32)).

Urinary organic acids showed moderately elevated hexanoylglycine, mildly increased suberylglycine and phenylpropionylglycine. No ketones and carboxylic acids.

DIFFERENTIAL DIAGNOSIS

- ▶ Short chain acyl-Coenzyme A (CoA) dehydrogenase deficiency
- ▶ Long chain acyl-CoA dehydrogenase deficiency
- ▶ Very long chain acyl-CoA dehydrogenase deficiency
- ▶ Reyes's syndrome
- ▶ Urea cycle disorders

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Trend of capillary blood glucose on admission

Figure 1 The trend of CBG during admission. Admitting CBG was 1 mmol/L. There were successive increments of the strength of the dextrose infusion to maintain normoglycaemia. Red arrow denotes administration of 2 mL/kg D10W bolus and subsequent D5NS infusion. Yellow arrow denotes bolus correction with D10W and change to D7.5NS. Green arrow denotes D10NS while dark arrow, D12.5NS. Refractory hypoglycaemia might be accounted for by inability of the process to proceed to electron transport chain and downregulation of gluconeogenesis. CBG, capillary blood glucose; D, dextrose; NS, 0.9% saline.

Figure 2 Fatty acid β oxidation. Fatty acids are oxidised in the mitochondria to generate acetyl-CoA which enters TCA cycle and NADPH and FADH₂, which are coenzymes used in electron transport chain. The pathophysiology of MCADD results from inability to carry out the first step of oxidation. Gluconeogenesis is shut down because it depends on the activity of the rate limiting enzyme pyruvate carboxylase to produce oxaloacetate, a reaction downregulated by diminished acetyl-CoA. CACT, carnitine-acylcarnitine translocase; CoA, Coenzyme A; CPT, carnitine palmitoyltransferase; ECHS, enoyl-CoA hydratase; ECT, enoyl-CoA isomerase; HADH, hydroxyacyl-CoA dehydrogenase; KAT, keto acyltransferase; LCAD, long chain acyl-CoA dehydrogenase; MCAD, medium chain acyl-CoA dehydrogenase; MTP, mitochondrial trifunctional protein; SCAD, short chain acyl-CoA dehydrogenase; TCA, tricarboxylic acid; VLCAD, very long chain acyl-CoA dehydrogenase.

- ▶ Organic acidurias
- ▶ Drug toxicity: aspirin, fluoroquinolones, quinine
- ▶ Primary carnitine deficiency
- ▶ Carnitine transporter defect
- ▶ Hereditary fructose intolerance
- ▶ Respiratory chain defects
- ▶ Defects in ketogenesis: HMG-CoA lyase deficiency, HMG-CoA synthase deficiency

TREATMENT

The treatment of hypoglycaemia in an emergency is through the intravenous route if cannulation is feasible; otherwise, glucogel can be put in the mouth. Severe hypoglycaemia can warrant intramuscular injection of glucagon in the absence of intravenous access. Maintaining euglycaemia with intravenous fluids until oral feeding is optimally established and is the standard protocol. This fortunately reverses symptoms in most cases. She was started on intravenous ceftriaxone but was discontinued after 48 hours following no evidence of infection on investigations. She needed up to 12.5% dextrose to maintain blood sugar within the range of 4 mmol/L (figure 1).

The main stay in the treatment of MCADD is avoidance of fasting and home care plan for caregivers in cases of illnesses.

OUTCOME AND FOLLOW-UP

The patient made a full recovery and has been doing quite well. She is being followed up by the metabolic team. Parents have been educated on type of diet with a home care plan during periods of illness (S.O.S 20%). She is currently on daily oral carnitine.

Her two older sisters were screened with acyl carnitine profile and urine organic acids; they appear not to have the disorder.

Parents were not screened for the mutation as they declined despite genetic counselling.

DISCUSSION

MCADD is an autosomal recessive metabolic disorder of mitochondrial fatty acid β oxidation (figure 2). MCAD is a homotrimer and shows its highest activity with octanoyl-CoA. It is the most common inherited disorder of mitochondrial fatty acid β oxidation. The overall frequency of the disorder is highest in northern Europe and has been estimated to range between 1:4900 and 1:17 000.^{1 2} Fatty acid β oxidation fuels hepatic ketogenesis, a major source of energy once hepatic glycogen stores become depleted.² In a typical clinical scenario, a previously healthy child with MCADD presents between the third month and the second year of life with hypoketotic hypoglycaemia, vomiting and lethargy, which can quickly progress to coma and death.² Acute episodes are generally triggered by a common illness or by prolonged fasting and liver disease is often seen at presentation. The prognosis of MCADD is excellent once the diagnosis is established and frequent feedings are instituted.² To prevent catabolic stress, patients are made to consume a carbohydrate-rich diet, carnitine supplements and prevented from fasting.³

Diagnosis of MCADD requires the integrated interpretation of array of tests, also considering the clinical status of the affected individual (acutely symptomatic vs asymptomatic) at the time of sample collection. Initial testing involves the hypoglycaemic screen which includes acylcarnitine (Guthrie card), urine organic acids, urine acylglycine analyses. The gold standard for diagnosis of fatty acid oxidation disorders is plasma acylcarnitine profile analysis performed by tandem mass spectrometry.⁴ Further confirmatory testing can be by genetic testing (ACADM mutation analysis or measurement of MCAD enzyme activity in leukocytes, fibroblasts).

Salter *et al*⁵ published a case in Ireland of a 2-year-old girl presenting to the emergency room unconscious and in cardiac arrest. She had severe hypoketotic hypoglycaemia and was subsequently confirmed MCADD.⁵ Liang *et al*⁶ published the first case of genetically confirmed MCADD in China, a case of a 2-year-old girl who presented with hepatomegaly and abnormal liver function following a common illness having been a previously well child.

In the index case, she was also an apparently healthy girl presenting with severe hypoglycaemia following persistent vomiting. Although, urine dipstick performed at the stage of acute decompensation showed ketonuria, further testing revealed the diagnosis which is a cause of hypoketotic hypoglycaemia. Before the definitive results became available, her case became somewhat confusing as she needed up to 12.5% dextrose to maintain blood glucose not <5 . An evolving metabolic disorder was entertained. The elevated levels of hexanoylcarnitine (C6), octanoylcarnitine (C8) and decanoylcarnitine (C10) with the urine organic acid pattern strengthened the diagnosis of MCADD in this patient. Therefore, the detection of ketonuria by routine urinalysis should not be taken as evidence against a possible diagnosis of MCADD. Her raised white cell count could have been accounted for by the metabolic stress. The values returned to baseline on repeat checks.

Major therapeutic goal is to reverse catabolism and sustain anabolism. Hypoglycaemia due to reduced gluconeogenesis and increased tissue glucose uptake is a major finding in MCADD.⁷ Herrema *et al*⁸ demonstrated in a study that enhanced

peripheral glucose uptake due to increased glucose consumption during energy deficiency appeared to be the major pathophysiological mechanism responsible for development of hypoglycaemia in MCADD.

L-carnitine may be helpful in MCADD, although this is controversial. L-carnitine was shown to reduce the number and severity of metabolic decompensation in some patients by correcting the secondary deficiencies of this compound and probably by its property of binding to the toxic accumulating metabolites, increasing their urinary excretion. L-carnitine may also restore acyl-CoA/CoA ratio that is necessary for crucial mitochondrial functions.^{9 10} On the other hand, another school of thought postulates that L-carnitine may not normalise tissue concentration of this compound and may induce the production of potentially toxic long chain acylcarnitines.¹¹

Patient's perspective

G had been a very well, happy child. I had never had any cause to worry about her since she was born. Her progressively worsening drowsiness on the day she was admitted gave me a fright. I became more worried when it was difficult to get her veins for a drip. Fortunately, that was settled but I felt something was not right as I heard the value of her blood sugar. She eventually came around after a day or so. I was getting ready for discharge as I was expecting my fourth baby. It was a huge shock when I got the news that she might have MCADD and the metabolic team in Dublin wanted her transferred. I was dissuaded from searching for information online but I was curious. It was saddening that it is actually part of the newborn screening in England but not in Ireland. Overall, I got a lot of support from the managing team. I was relieved when my 2 older daughters were screened and said not to have the disorder. Am still grateful that this condition is very manageable and I have had no cause to visit the hospital till date. I feel very confident in dealing with the sick day rules as I was taught. Finally, it will be ok if the screening is incorporated in Ireland.

Learning points

- ▶ Early diagnosis of medium-chain acyl-Coenzyme A dehydrogenase deficiency (MCADD) helps to start simple treatment aimed at preventing further decompensation.
- ▶ MCADD satisfies the major criteria for newborn screening in Ireland.
- ▶ Hypoglycaemic screen is necessary for all children presenting with blood glucose level below 2.6 mmol/L.
- ▶ Detection of ketonuria by routine urinalysis should not be taken as evidence against a possible diagnosis of MCAD deficiency.

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REFERENCES

- 1 Schatz UA, Ensenauer R. The clinical manifestations of MCAD deficiency: challenges towards adulthood in the screened population. *J Inherit Metab Dis* 2010;33:513–20.
- 2 Maclean K, Rinaldo P. Medium-chain acyl-Coenzyme A dehydrogenase deficiency. <http://www.ncbi.nlm.nih.gov/books/NBK1424>
- 3 Derks TG, van Spronsen FJ, Rake JP, *et al.* Safe and unsafe duration of fasting for children with MCADD. *Eur J Paediatr* 2007;166:5–11.
- 4 Van Hove JL, Zhang W, Kahler SG, *et al.* MCAD: diagnosis by acylcarnitine analysis on blood. *Am J Hum Genet* 1993;52:958–66.
- 5 Salter N, Quin G, Tracy E. Cardiac arrest in infancy: don't forget blood glucose! *Emerg Med J* 2010;27:720–1.
- 6 Liang C, Jiang M, Sheng H, *et al.* First case report of MCADD in China. *J Pediatr Endocrinol Metab* 2015;28:681–4.
- 7 Bastin J. Regulation of mitochondrial fatty acid-beta oxidation in human: what can we learn from inborn fatty acid beta-oxidation deficiencies?. *Biochimie* 2014;96:113–20.
- 8 Herrema H, Derks TG, van Dijk TH, *et al.* Disturbed hepatic carbohydrate management during high metabolic demand in medium-chain acyl-CoA dehydrogenase deficiency mice. *Hepatology* 2008;47:1894–904.
- 9 Lee PJ, Harrison EL, Jones MG, *et al.* L-carnitine and exercise tolerance in MCADD: a pilot study. *J Inherit Metab Dis* 2005;28:141–52.
- 10 Derks TG, Toww CM, Ribas GS, *et al.* Experimental evidence for protein oxidative damage and altered antioxidant defense in patients with MCADD. *J Inherit Metab Dis* 2014;37:783–9.
- 11 Spiekerkoetter U, Bastin J, Gillingham M, *et al.* Current issues regarding treatment of mitochondrial fatty acid oxidation disorders. *J Inherit Metab Dis* 2010;33:551–61.

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