Cyclic vomiting syndrome masking a fatal metabolic disease

Abstract:

This case describes a rare disorder of fatty acid oxidation (Multiple Acyl Coenzyme A Dehydrogenase Deficiency) presenting with a raised anion gap metabolic acidosis, non-ketotic hypoglycaemia and multi-organ failure in a young woman with a previous diagnosis of Cyclical Vomiting Syndrome.

Non-ketotic hypoglycaemia in the presence of significant acidosis may represent an undiagnosed rare disorder of fatty acid oxidation. Congenital disorders may present outside of early childhood, in adolescence or beyond and all practitioners should be aware of these rare disorders as a cause of unexplained acidosis.

Introduction:

Fatty acid oxidation disorders (FAOD) are rare, but are being more frequently diagnosed with increasing sophistication and accessibility of detection methods. These disorders usually present in childhood but may present in adolescence or early adult life in those with less severe phenotypes. We present a case of Multiple Acyl CoA Dehydrogenase Deficiency (MADD) in a young critically ill patient.

These disorders are an unusual cause of acidaemia in the intensive care unit, but should be considered early in the differential diagnosis and work up of unexplained acidosis. Due to their relatively rare incidence, and wide range of presentations, these diseases may be missed or misdiagnosed.

Case History:

A 20 year old female presented to the Emergency Department with a one- week history of sore throat, nausea, right flank pain, lethargy and anorexia. Background history was notable for Cyclical Vomiting Syndrome (CVS), diagnosed 12 years previously, and chronic fatigue commencing in her teens.

Assessment showed clinical evidence of dehydration including sinus tachycardia of 140bpm, with dry mucous membranes. Her blood pressure was 116/67mmHg. Abdomen was soft with slight tenderness in the right hypochondrion. She was initially treated with intravenous 0.9% Saline and anti-emetics.

Ten hours later she had a witnessed cardiac arrest with an initial rhythm of Ventricular Fibrillation. She was successfully resuscitated, with a return of spontaneous circulation after 16 minutes.

Investigations were as shown in Table 1. Pre-arrest investigations were notable only for a WCC of 16×10^9 . Arterial blood gas analysis was not initially performed as the clinical condition did not warrant it; presenting lactate level is unknown. Post resuscitation she had an acidaemia with pH of 7.18. Anion gap was elevated at 22. There was marked hypoglycaemia with blood glucose of 1.3mmol/L.

Organ support was commenced including mechanical ventilation, renal replacement therapy and vasopressor infusions. Persistent hypoglycaemia was treated with 5% dextrose infusions, and boluses of 50% dextrose. She was treated empirically with broad-spectrum antibiotics, with anti- fungal and anti-viral

cover. No source of sepsis was found, despite multiple investigations. Abdominal ultrasound and CT of abdomen showed fatty infiltration of the liver, with ascites. Liver function tests were abnormal and continued to deteriorate. Throughout her critical illness she had a profound metabolic acidosis, which did not respond to any treatment. Vasopressor therapy rapidly escalated despite massive fluid resuscitation.

Unfortunately, 72 hours after presentation, fulminant Multi-Organ Failure had evolved, refractory to aggressive treatment, and the patient died.

Post-Mortem Results:

Postmortem examination was consistent with multi-organ failure. Post mortem findings were significant in pointing towards an underlying disorder of Fatty Acid Metabolism. There was evidence of abnormal fat storage seen in skeletal muscle, liver and cardiac muscle. There was also an unusual pattern of vacuolar change in the granular layer of the cerebellum, without axonal spheroid formation (Figure 1). Skeletal muscle fibres were noted to hold excess sarcoplasmic fat with multiple intra-sarcoplasmic vacuoles in Type 1 fibres with atrophy. There was diffuse, bi- hemispheric cerebral oedema.

Abnormal Lipid Storage involving skeletal muscle, heart muscle, liver and cerebellum suggested a diagnosis of Multiple Acyl Co-enzyme A Dehydrogenase Deficiency (MADD). Unfortunately no urine or blood samples were available for biochemical analysis. The patient's original newborn screening dried blood spot was analysed for acylcarnitine species but was non-diagnostic. Molecular

analysis of the *ETFDH* gene from DNA extracted from paraffin embedded muscle and the newborn blood spot found compound heterozygosity for the following pathogenic mutations: c.51_52ins (p.ala18cysfsX5) and c.1367C>T (p.pro456leu) confirming a diagnosis of MADD. Carrier status was confirmed on parental DNA.

Background history (obtained from her parents in later months):

The patient was born at term and there were no neonatal concerns. At the age of 6 months and again at 12 months she was admitted to hospital acutely unwell, limp and lifeless; she recovered fully following treatment with IV fluids and antibiotics. She had no fever and no infection source was found on either occasion.

She was diagnosed with Cyclical Vomiting Syndrome at age 9 years and had episodic vomiting once every 6 weeks or so; for some of these episodes she required hospital admission for treatment with intravenous dextrose. She had documented ketones in her urine during some of these admissions, only on one occasion was mild hypoglycaemia noted. In her late teens she had a number of episodes of collapse, and she may have had a seizure on one occasion. She was reported to drink much high sugar drinks (Lucozade ®) and had unusual eating patterns without definite protein avoidance. In the weeks before this presentation, she had been unusually fatigued, and had neck weakness. She had pronounced lethargy and exercise intolerance. She had been recently transferred from the local paediatric service to an adult physician for monitoring of her symptoms, though these had been attributed to Cyclical Vomiting

Syndrome.

Informed consent has been obtained from her parents for publication of her case. Local Ethics Committee Board approval was sought and waived.

Discussion:

Raised Anion Gap Metabolic Acidoses are caused by the addition of endogenous or exogenous acids to the system. Common causes in critically ill patients are production of lactic acids, ketoacids (usually diabetic or alcoholic), or renal failure (endogenous acidosis), or the addition of exogenous acids (salicylates, methanol, ethylene glycol). In this case an initial toxicology screen was negative for alcohol and salicylates. The possibility of ethylene glycol or methanol poisoning was considered unlikely from the presenting history and post mortem analysis of blood samples out-ruled it. Renal replacement therapy was commenced for treatment of acidosis rather than renal failure and urinary ketones were not present. Though lactate was elevated initially and later in the course of the illness, it was cleared at some stages by CVVH despite persistent acidosis, and was thought that the combination of acidosis with non-ketotic hypoglycaemia on presentation was a consequence of tissue hypoxia rather than a causative factor.

The clinical course of our patient was rapidly progressive and fulminant multi-organ failure supervened while investigations were ongoing. A first presentation of this disorder in adulthood is extremely rare but metabolic disease should be considered in all cases of refractory hypoglycaemia with acidosis, ketotic or non-ketotic. Urinary organic acid analysis and blood acylcarnitine profile may yield the diagnosis during an episode of decompensation, however these may be normal when the patient is well.

The hypoglycemia in Fatty Acid Oxidation Disorders is most easily

explained by the inability of affected patients to use fatty acids as a fuel as a substitute for glucose. This normally occurs during fasting. In MADD, multiple different dehydrogenase reactions in the mitochondrial electron chain are affected with at least 12 different flavoprotein dehydrogenases being implicated. Many patients with MADD have been shown to have mutations in *ETFA*, *ETFB* or *ETFDH*.¹ These genes code for flavoprotein dehydrogenases.

Multiple acyl-coenzyme A dehydrogenase deficiency (MADD, OMIM number: #231680, also known as Glutaric aciduria type II) is an autosomal recessive, mitochondrial organic acid disorder. There are 3 distinct phenotypes described: Type 1 is associated with congenital abnormalities and is characterised by hypoglycemic encephalopathy associated with hypotonia, metabolic acidosis and organomegaly. Death in infancy is common.² Type 2 is also diagnosed in early childhood, but there are no congenital abnormalities present. The late onset form (Type 3), as in this case, is typically characterised by myopathy together with features of hepatic insufficiency. There may be acute episodes with increased weakness, vomiting, hypoglycaemia and acidosis. It has a heterogeneous manifestation and may be diagnosed in childhood or adult life, though usually before the age of fifteen. It has been found in some series to be responsive to Riboflavin and Ubiquinone (Coenzyme Q10) and L-carnitine treatments.¹ In all forms, the pathophysiology of this disorder involves the development of episodic hypoketotic hypoglycemia provoked by catabolic stress. This stress may have an infective origin. Clinically, episodes may present as coma, multiple organ failure or muscle weakness. A high mortality has been

reported.

Due to its extreme rarity the exact incidence of MADD is unknown. It may have a higher incidence in Asia, where many of the case reports originate. Genetic analysis of 19 consecutive patients with Lipid Storage Myopathy patients collected from 1995-2007 suggests that the majority of Chinese patients with Lipid Storage Myopathy are caused by a mild type of MADD, due to *ETFDH* gene mutations.⁵ Coenzyme Q10 or Ubiquinone deficiencies may be allelic with MADD and the myopathic form of MADD has been described in patients who had initially been diagnosed with isolated Q10 deficiency associated with myopathy.

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Traditionally diagnosis by is the gas chromatographic/mass spectrometric analysis of urinary organic acids. Diagnosis may be achieved in newborns by the detection of elevated plasma long chain acylcarnitine species in dried blood spots. The adult forms may be missed in the well newborn. Mutation analysis is a superior tool for specific diagnosis particularly in milder forms where biochemical testing may be normal when the patient is well.

This case was positive for 2 heterogeneous mutations of the *ETFDH* gene, both pathogenic. The patient's parents have both been confirmed as carriers. DNA extracted from paraffin-embedded muscle and patient's 20+year old original newborn screening card was used for the genetic analysis. Post-mortem diagnosis of MADD by mutation analysis in a patient who was critically ill has previously been described.⁴

The association between Cyclical Vomiting Syndrome and MADD has

been made before⁶, though whether this represents a true association, or whether the very rare MADD is inadvertently diagnosed as the more common CVS is uncertain (Irish incidence 3.15 cases per 100,000 children.⁷)

One study⁸ looking at alternative diagnoses presenting as CVS in 225 cases, found that 88% were in keeping with idiopathic cyclical vomiting. In this case series one patients (0.44%) had a diagnosis of a fatty acid oxidation defect (Very Long Chain Acetyl CoA Dehydrogenase deficiency) subsequently made. Interestingly, some patients with a diagnosis of CVS may respond to treatment with L-carnitine^{9,10} which is a well documented treatment for MADD.⁵ One study¹ of 15 patients with riboflavin responsive MADD, all of whom had an *ETFDH* mutation, demonstrated that 5 also had CVS.

Early diagnosis is important as prophylactic dietary treatments and emergency sick-day guidelines may prevent life-threatening metabolic crises⁵. Genetic counseling is essential for affected families. Patients diagnosed acutely with MADD should be treated with riboflavin, carnitine and Coenzyme Q10 supplementation, and low-fat, low-protein diet. Patients known to have MADD who decompensate should have similar supplementation, while organ support, if necessary, is ongoing.

Conclusions:

Non-ketotic hypoglycaemia in the presence of significant acidosis may represent an undiagnosed disorder of fatty acid oxidation or MADD. Although these conditions are extremely rare they should be considered in the differential diagnosis, particularly in children. Urgent investigation may require referral to the local metabolic service. These diseases will usually present in, but are not exclusive to childhood. First presentation may lead rapidly to multi organ failure. Less severe phenotypes may have an indolent clinical course until decompensation, which may be sudden and catastrophic as in this case. Infection is often a trigger for decompensation. Treatment includes enzyme supplementation and supportive therapies. In patients in whom the diagnosis is not made, post-mortem genetic analysis can play a valuable role. Blood, urine and DNA samples should be preserved in these cases.

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Investigation	Results	Result	Normal Reference range
	Pre Resuscitation	Post Resuscitation	
Arterial Blood Gas: (FiO2 1.0)			
pH		7.16	7.35 – 7.45
BE		-10 mmol/L	-2 – +2 mmol/L
HCO3-		15 mmol/L	22 – 26mmol/L
pCO2		4.5 kPa	4.67-6.0 kPa
pO2		22 kPa	10.67-13.03 kPa
Anion Gap		25	12 +/- 4
Lactate		6.1 mmol/L	0 – 2.4mmol/L
Full Blood Count	WCC 14.7 Hb 14.7 Platelets 274	WCC 10.9 Hb 11.5 Platelets 236	4.0 -10-0 x10 ⁹ /L 13.5 – 17.5 g/dL 150 – 400 x 10 ⁹ /L
Liver Function Tests	AST 376 ALT 426 Albumin 43 Alkaline	AST 390 ALT 519 Albumin 34 Alkaline	<37 IU/L <45 IU/L 33 – 48 g/L 40 – 130 IU/L

Measured Anions	Phosphatase 62	Phosphatase 54	
	GGT 49	GGT 43	<49 IU/L
		INR 2.1	0.9 – 1.15
		Ketones negative	
	Urea 7.0	Urea 8.0	2.5 – 7.0 mmol/L
Serum glucose		Toxicology Screen (salicylates, alcohol, paracetamol) negative	
		Lactate 6.1	0 – 2.4 mmol/L
		1.4	
Creatinine Kinase		650	3.5 – 5.0 mmol/L
			<140 IU/L
CT of Thorax, Abdomen, Pelvis		Collapsed lung bases bilaterally, Normal bowel, normal pelvis, fatty liver	

US Abdomen		Fatty liver, no ascites	

Table 1: Results of initial investigations

Figure 1: Cerebellar Vacuolar Change

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