CASE REPORT

Fat oxidation defect presenting with overwhelming ketonuria

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Ketonuria accompanying hypoglycaemia is conventionally thought to exclude fat oxidation defects. We describe a 2 year old girl with hypoglycaemic encephalopathy in whom a diagnosis of very long chain acyl CoA dehydrogenase deficiency was suggested on the basis of acylcarnitine analysis despite massive ketonuria.

Initial evaluation of a child presenting with hypoglycaemia includes urinalysis for ketones. Presence of ketones in the urine is conventionally thought to exclude inherited fat oxidation defects because enzymatic conversion of free fatty acids to ketones is blocked. We describe a child who presented with overwhelming ketonuria. A presumptive diagnosis of very long chain acyl CoA dehydrogenase deficiency (VLCADD) was made using analysis of plasma acylcarnitines; the diagnosis was subsequently confirmed by enzymology and genotyping.

CASE REPORT

A previously healthy first child of non-consanguineous parents presented aged 2 years with an encephalopathic illness precipitated by protracted vomiting. The liver was 5 cm palpable. Reflexes were brisk and plantar responses extensor. She was acidotic (pH 7.08, base deficit –15.3) and hypoglycaemic (glucose 1.7 mmol/l). Urinary organic acid analysis revealed massive ketonuria, with significant lactic aciduria, and dicarboxylic and 3-hydroxydicarboxylic aciduria. The pattern was reported as consistent with severe and prolonged fasting with possible infection. A fat oxidation disorder was not considered because of the degree of ketosis. Serum creatine kinase activity was increased (5373 U/l; normal <235 U/l), but alanine aminotransferase activity was within the normal range (49 U/l; normal 0–55 U/l). Scans (precursors of m/z 85 from m/z 150–450) for free carnitine and acylcarnitines were performed on underivatized plasma using flow injection electrospray tandem mass spectrometry; analysis time <2 minutes. Plasma free carnitine was slightly depleted (19.2 µmol/l; normal >25 µmol/l) but there was a significant elevation of tetradecenylcarnitine (1.69 µmol/l; normal <0.09) suggesting a diagnosis of VLCADD. This was subsequently confirmed on the basis of cultured fibroblast enzyme activity (oleate oxidation 18% of simultaneous controls) and genotype (compound heterozygote with deletion 644–677 in exon 8 and V234A mutation in exon 9). Following this episode she has residual neurological impairment but is continuing to improve.

DISCUSSION

Inherited disorders of fatty acid oxidation classically present with hypoketotic hypoglycaemic coma induced by fasting and often precipitated by acute infection.^{1,2} VLCADD is a recently identified autosomal recessive condition³ that usually presents

early in life with encephalopathy, hypoglycaemia, hypertrophic cardiomyopathy, and liver failure. Milder phenotypes with later presentation have been described.^{2,4} The anticipated biochemical abnormalities in the fat oxidation disorders include hypoketotic hypoglycaemia, dicarboxylic aciduria, and characteristic accumulation of specific acylcarnitines. However, it is now recognised that in medium chain acyl CoA dehydrogenase deficiency (MCADD) ketonuria may accompany hypoglycaemia, albeit at an inappropriately low level. This is explained by residual enzyme activity. In VLCADD the primary defect is in β -oxidation of unsaturated fatty acids, hence the accumulation of tetradecenylcarnitine, but oxidation of saturated fatty acids is relatively unimpaired and ketone production may continue. Urine organic acid analysis is particularly useful in the diagnosis of MCADD because of the presence of hexanoylglycine, but in other fat oxidation disorders there are no specific diagnostic metabolites. Dicarboxylic aciduria and/or 3-hydroxydicarboxylic aciduria in the absence of ketonuria have been considered diagnostically useful, but they are relatively non-specific and several reports have documented only mildly increased or even normal dicarboxylic acid concentrations during decompensation.⁴ Previously, and despite well documented limitations, urine organic acid analysis has been the usual means of investigating the child with a suspected fat oxidation defect. In this case urine organic acid analysis was not only uninformative but also misleading, while analysis of plasma acylcarnitines allowed prompt diagnosis.

Plasma acylcarnitines should be considered a mandatory first line investigation of any child presenting with acute hypoglycaemic encephalopathy, even in the presence of massive ketonuria. A further point of importance is that although plasma acylcarnitines show characteristic patterns of elevation during decompensation, they may be within the normal range at other times. Securing appropriate samples at the time of presentation is therefore essential.

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Abbreviations: MCADD, medium chain acyl CoA dehydrogenase deficiency; VLCADD, very long chain acyl CoA dehydrogenase deficiency

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COMMENTARY

KETOACIDOSIS—A TRAP FOR THE UNWARY?

Hypoglycaemia in childhood has many potential causes. The majority of cases result from idiopathic hyperketotic hypoglycaemia—an accelerated physiological response to fasting, with no clearly identified biochemical defect. Ketones are produced when hepatic production of acetyl CoA exceeds its utilisation. Postprandially as glucose absorption declines and glucagon concentrations rise, insulin concentrations drop; this removes inhibition on adipose tissue lipoprotein lipase resulting in free fatty acid release. Many tissues preferentially oxidise fatty acid. The brain requires glucose but can adapt over days to use ketones as an oxidative substrate. Glycogenolysis and gluconeogenesis maintain glucose concentrations. Thus homeostasis involves coordination of multiple metabolic and endocrine pathways.

Adenovirus, influenza, or gastroenterological infections frequently precipitate hypoglycaemia. The commonest metabolic disorder by far is the fatty acid oxidation defect medium chain acyl CoA dehydrogenase deficiency (incidence 1 in 10 000), often described as a “non-ketotic” illness, and, even in the current 5th edition of *Forfar and Arneil*,¹ as producing “recurrent hypoglycaemia, classically hypoketotic”.

In fact, all fatty acid oxidation defects will permit production of ketones, though this is relatively reduced compared to the free fatty acid concentration, such that in hypoglycaemia the ratio of beta-hydroxybutyrate to free fatty acid should be greater than 0.7.² The child reported by Wraige *et al* developed severe ketoacidosis when acutely ill with hypoglycaemia as a result of an underlying diagnosis of very long chain acyl CoA dehydrogenase (VLCAD) deficiency. The authors make the important point that the presence of severe ketosis does not exclude a diagnosis of fat oxidation disorder. We wish to extend that observation so that the presence of ketosis does not allow a falsely complacent diagnosis of “ketotic hypoglycaemia”.

Other conditions which can present with ketotic hypoglycaemia are: (1) late onset form of maple syrup urine disease; (2) organic acidemia, particularly methylmalonic and isovaleric acidemia; (3) multiple carboxylase deficiency; (4)

defects of gluconeogenesis, such as glycogen storage disease type 1a where hepatomegaly is present; and (5) endocrine disorders, for example, absent catecholamine response, or hypoglucocorticoid states. Occasional reports appear where ketonuria has completely masked an underlying disorder. Carpenter *et al* reported a case of holocarboxylase deficiency in a child with vomiting and diarrhoea.³ Only a second organic acid analysis showed findings compatible with holocarboxylase deficiency, the first one being dominated by ketonuria. Two further causes of hyperketosis with acidosis, but without hypoglycaemia, are diabetic ketoacidosis and the rare ketolytic defects, especially mitochondrial acetoacetyl CoA thiolase deficiency.⁴

What clues are available to selectively identify the at-risk child in this clinical scenario? An unwell child with drowsiness secondary to hypoglycaemia should rapidly respond to oral or intravenous glucose. When the paediatrician or carer remains concerned that it took time for the child's drowsiness to clear, then further investigations are appropriate. Important basic biochemical assessment beyond hypoglycaemia should include assessment of: acidosis (clue to organic acidosis), creatine kinase (clue to VLCAD), beta-hydroxybutyrate/free fatty acid ratio (below 0.7 being suspicious of fatty acid oxidation defect), ammonia (raised in fatty or organic acid disorders), and cortisol (confirming, over 500 nmol/l). The classical low sodium of Addison's disease may not be present in a hypoglucocorticoid state, for example, congenital adrenal hypoplasia. While acyl carnitine profiles offer advantages, they can be hard to obtain at present. Free plasma carnitine by radioenzymatic methods is more readily available, with results under 15 μ mol/l being significant. It is important to ask the laboratory to freeze any unused plasma from the initial presentation for possible further studies.

Where concerns arise, careful discussion with a paediatrician in metabolic medicine or a paediatric biochemist should ensue. Idiopathic ketotic hypoglycaemia remains a diagnosis of exclusion.

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