

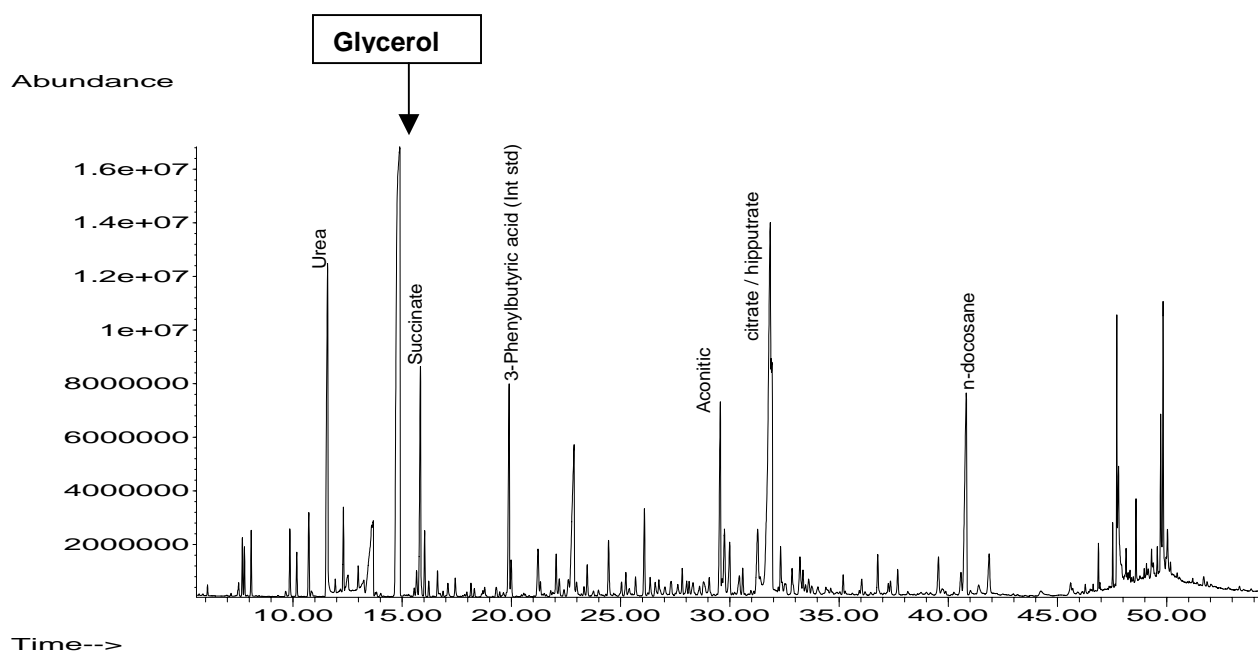
A Case of Isolated Glycerol Kinase Deficiency

Case History

The patient was born at term to non-consanguineous parents following a normal pregnancy, and there was no past medical history of note. He presented at 2.5 years of age following a one day history of diarrhoea, vomiting and pyrexia. On arrival at the Accident and Emergency department he was floppy and unresponsive, except to painful stimuli, however there were no abnormal movements. He was maintaining his airways and breathing normally. The laboratory blood glucose concentration was 1 mmol/L. He was treated with intravenous glucose (10% dextrose bolus of 5 ml/kg) and recovered within 10 minutes. He was treated for suspected gastroenteritis and given antibiotics for possible tonsillitis.

Preliminary Laboratory Investigations

As there was no clear explanation for the **profound hypoglycaemia**, metabolic investigations were carried out to determine whether there was an underlying metabolic cause. Analysis of urinary organic acids showed **excessive glycerol in the urine**, along with an increase in ketones (butyrate and acetoacetate) and dicarboxylic acids. Repeated analysis without a period of starvation showed consistently increased glycerol excretion, but on this occasion no ketones or dicarboxylic acids.



Glycerol is a common component of many 'over the counter' medicines and ointments which can lead to a false positive results. The finding of increased glycerol excretion should therefore be confirmed in a subsequent sample as it was in this case. Urine and plasma amino acids showed no significant abnormality and acyl carnitine analysis was normal indicating that a fatty acid oxidation disorder was unlikely.

Differential Diagnosis

Possible causes of the significant glyceroluria were felt to be fructose-1,6-bisphosphatase deficiency, glycerol kinase deficiency and glycerol intolerance syndrome. Fructose-1,6-bisphosphatase deficiency would however be expected to be accompanied by lactic acidemia, of which there was no mention, and would not usually result in such a high level of glycerol in the urine. Glycerol Intolerance Syndrome presents in a similar way to glycerol kinase deficiency but glycerol kinase activity is normal.

Recommended Further Investigations and Results of Further Testing

White blood cell fructose biphosphatase activity was measured and found to be normal (0.9 umol/min/g; Ref >0.3). **Glycerol Kinase Deficiency** was confirmed by enzyme assay in fibroblasts in which glycerol kinase activity was undetectable (Ref : 0.98 – 2.07 nkat/g protein). In view of the association with adrenal hypoplasia and Duchenne muscular dystrophy, adrenal function was assessed and CK measured. The plasma creatine kinase activity was normal (77 U/l). A random cortisol was measured as 323 nmol/L and a short synacthen test indicated an adequate adrenal reserve. **Isolated Glycerol Kinase Deficiency** was therefore diagnosed in this patient, with hypoglycaemia as the only presenting feature.

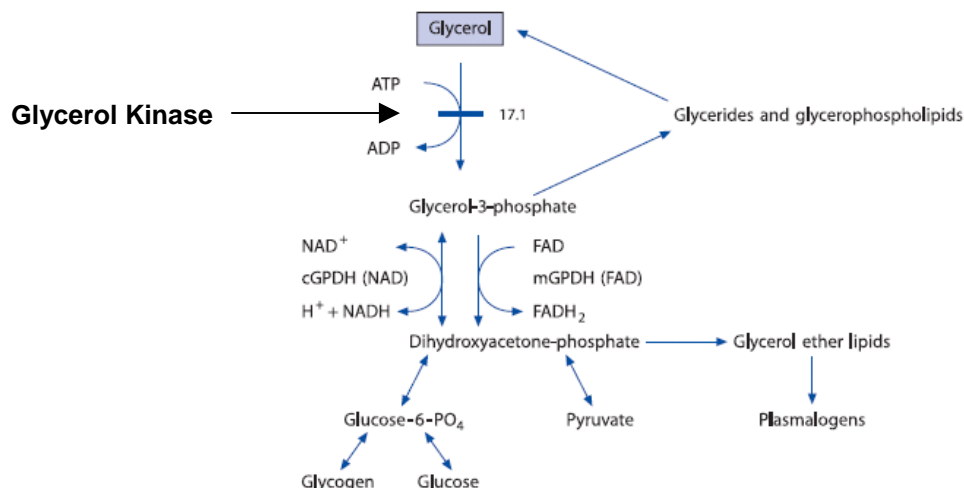
Treatment & Monitoring

The patient has been managed with an 'emergency regime' involving regular high carbohydrate drinks during intercurrent illness when the patient is vulnerable due to catabolism and breakdown of fat releasing glycerol. He is now aged 5 years, has had no further episodes of hypoglycaemia and is developing normally.

Overview of Disease

Glycerol kinase deficiency (GKD) is an X-linked inherited disorder of glycerol metabolism. It can occur in an isolated form or as part of a contiguous gene syndrome involving the glycerol kinase gene along with the gene loci for congenital adrenal hypoplasia and / or Duchenne muscular dystrophy. Many cases of the isolated form are asymptomatic and may only be picked up on the basis of an incidental finding of pseudohypertriglyceridaemia in adulthood. In some cases, however, isolated GKD has presented in the juvenile period with symptoms including vomiting, acidaemia and encephalopathy. There are a few reports of hypoglycaemia occurring as a presenting feature in these patients.

The pathway of glycerol metabolism, indicating the block due to glycerol kinase deficiency is shown below. Sources of glycerol include endogenous breakdown of triglycerides and other glycerolipids, production from glucose/protein/lactate/pyruvate (glycerolneogenesis) and exogenous dietary fat intake. Glycerol acts as a substrate for gluconeogenesis in the liver and serves as a precursor for the production of glycerophospholipids. Glycerol kinase catalyses the initial step in the metabolism of glycerol - phosphorylation of glycerol by ATP to produce Glycerol-3-phosphate.



Discussion

There appears to be a high degree of heterogeneity and phenotypic variation in patients with isolated GKD. This case confirms the previously reported association in some patients between isolated GKD and a tendency towards hypoglycaemia. In common with other reported cases the hypoglycaemia occurred following a period of fasting / illness. Patients presented with varying degrees of hypoglycaemic symptoms and all recovered with administration of IV glucose. The presenting episode seen in this patient appears milder than that seen in previous patients, for example there was no reported metabolic acidosis or seizures. In addition, previous reports document repeated hospital admissions, whereas this patient has been well controlled since presentation and has had no further episodes. This supports the findings from follow up studies in previous cases, that patients develop normally and that symptoms related to isolated GKD improve with age.

The mechanism of hypoglycaemia in these patients has not yet been elucidated. One suggested mechanism is that low glucose levels occur due to the direct defect in gluconeogenesis. In the non-fasting state the reliance on hepatic gluconeogenesis is minimal, however during a prolonged catabolic state hepatic glycogen is depleted and hepatic glucose output becomes dependent on gluconeogenesis. In adults the use of glycerol as a gluconeogenic substrate accounts for approximately 1/5 of hepatic glucose output. In children this dependence is thought to be of at least the same magnitude. Therefore, a deficiency of glycerol kinase, resulting in the failure to utilise glycerol as a gluconeogenic substrate during the fasting state, may lead to hypoglycaemia. This hypothesis is supported by the tendency for symptoms to improve with age as the metabolic demand on the liver is reduced. It is also possible that there are effects on intermediary metabolism. The similarity of symptoms to patients with glycerol intolerance has led to the suggestion that symptoms may be due to direct toxic effects of high levels of glycerol, perhaps by interfering with the cellular utilisation of glucose. Susceptibility during illness may therefore reflect the fact that as a consequence of increased catabolism there is breakdown of fat producing an excess of glycerol. Further work needs to be done in order to establish which of these mechanisms are responsible.

Pseudohypertriglyceridaemia in glycerol kinase deficiency occurs due to an increase in free glycerol in the blood. In glycerol kinase deficiency serum glycerol levels between 1.8 and 8.3 mmol/L have been reported (Ref: 0.02 – 0.27). High levels of free glycerol interfere with the routine measurement of triglycerides by chemical and enzymatic assays which are based in the quantitation of glycerol liberated by hydrolysis. A falsely elevated result would not occur in methods which rely on solvent extraction and colorimetry. The finding of pseudohypertriglyceridaemia in glycerol kinase deficiency is important, particularly in a district general hospital where organic acid analysis is not carried out, as this may be the first diagnostic clue to the disorder. It is also important to consider when interpreting lipid results in known patients to prevent unnecessary investigation of hypertriglyceridaemia, and in the differential diagnosis of apparent hypertriglyceridaemia in adults who may potentially have asymptomatic glycerol kinase deficiency.

References

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Patient Confidentiality

Permission has been obtained from the patient's parents for this case to appear on the MetBioNet website.