Investigations of a hypoglycaemic infant

Presentation

- A three year old female patient, presented via the Paediatric Emergency Department
- A 3 week history of vomiting and diarrhoea, the vomiting had increased two days before admission
- Prior to admission, she had episodes of being rigid and sticking out her tongue, back arching, hallucinations and her eyes had been rolling
- Clinical examination showed capillary refill time of 4 seconds, suggesting dehydration and basal crackle in lower left lung
- Full term normal vaginal delivery, no problems during pregnancy or birth. No feeding problems
- Only current medication was Calpol
- Working initial diagnosis of gastroenteritis

Initial investigations

Test	Result	Reference range
Sodium	138	135 – 145 mmol/L
Potassium	3.9	3.5 – 5.3 mmol/L
Urea	10.8	2 – 6 mmol/L
Creatinine	54	10 – 70 µmol/L
ALT	317	Up to 50 U/L
Total Bilirubin	5	Up to 17 µmol/L
ALP	115	80 – 300 U/L
GGT	25	Up to 70 U/L
Albumin	29	24 – 48 g/L
CRP	13	Up to 5 g/L
Glucose	0.7	3- 5 mmol/L
Ammonia	128	Up to 40 µmol/L
Urine ketones	+	
Lactate	1	0.6 – 2.4 mmol/L

- Serum sample taken and saved for further investigations
- Urine sample collected (prior to treatment) for an inborn errors of metabolism screen
- Raised white cells and neutrophils

Differential Diagnosis of hypoglycaemia in neonates and children

Endocrine

- Hyperinsulinism
- Adrenal insufficiency
- Hypopituitarism
- Growth Hormone Deficiency
- Hypothyroidism

Metabolic

- Disorders of Fatty Acid Oxidation and Carnitine Transport
- Disorders of Carbohydrate Metabolism
- Disorders of Organic Acid Metabolism
- Disorders of Gluconeogenesis

Other Causes

- Neonatal complications: prematurity, birth asphyxia, congenital heart defects, infants of diabetic mother – secondary hyperinsulinism
- Drug Related: insulin, alcohol, aspirin, chemotherapy
- Liver and multi-organ failure
- Sepsis, Gastroenteritis

Idiopathic ketotic hypoglycaemia

- The most common cause for hypoglycaemia in children after the neonatal period is idiopathic ketotic hypoglycaemia. This is usually precipitated by an often relatively mild illness.

Follow up

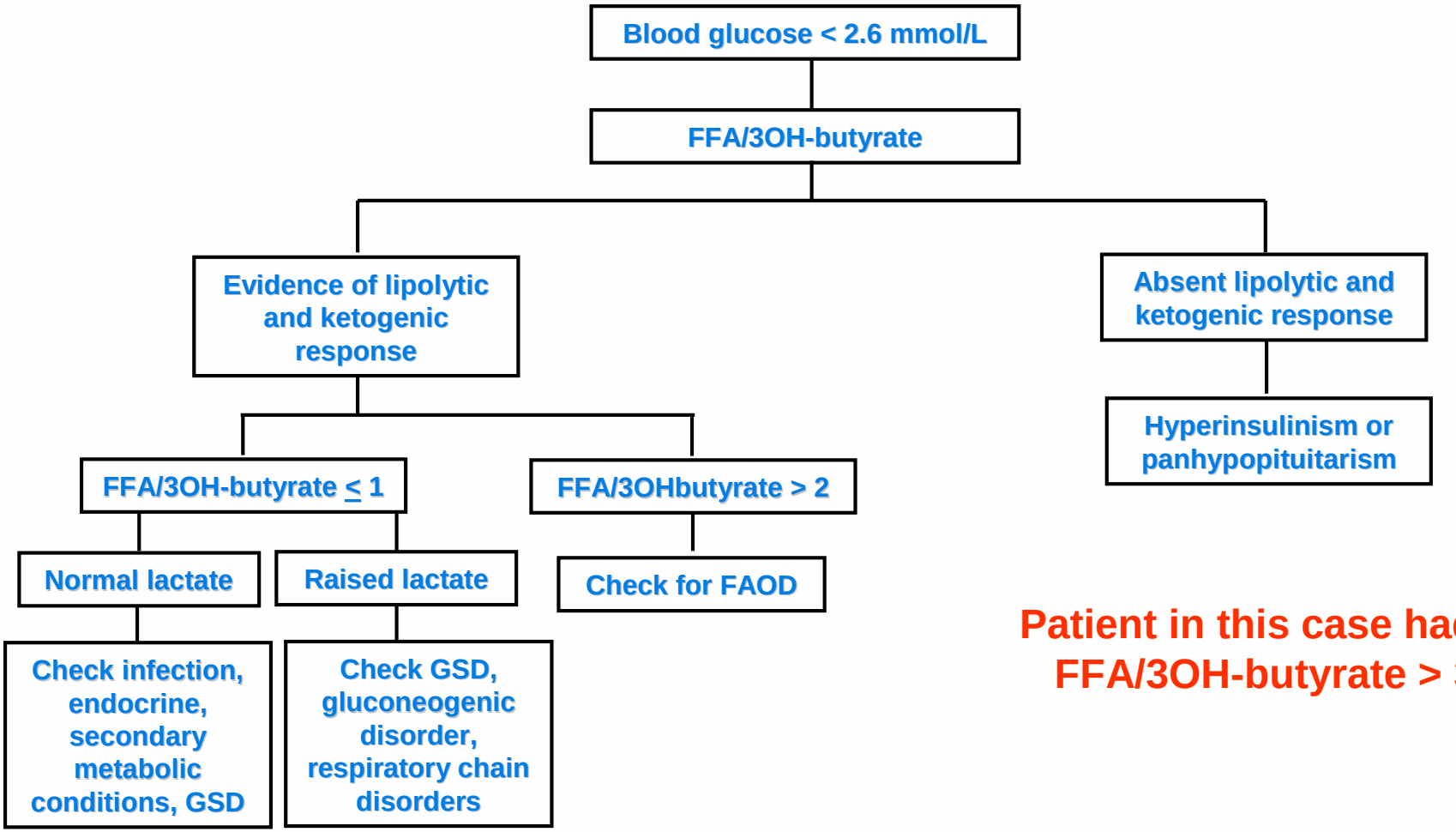
Test	Result	Reference range
ALT	324	Up to 50 U/L
Glucose	4.7	3- 5 mmol/L
Ammonia	9	Up to 40 µmol/L
Free Fatty Acids	0.912	(0.1 – 0.9 mmol/L)
D-3-Hydroxybutyrate	0.27	0.03 – 0.3 mmol/L
FFA/3-Hydroxybutyrate ratio	3.38	Ratio ≤ 1 appropriate lipolytic and ketogenic response to hypoglycaemia
Cortisol	>1400 nmol/L	A normal stress response
Insulin	Undetectable	

Samples taken when hypoglycaemic

- Patient given 5mL/kg 10 % dextrose to normalise glucose
- On repeat, glucose was 4.7 mmol/L and ammonia 9 µmol/L
- Further tests suggested no endocrine abnormality
- Maintained on 0.45 % normal saline with 5 % dextrose
- Patient alert, chest clear. Three days post-admission antibiotics were stopped as blood cultures were negative

FFA to 3-OH butyrate ratio

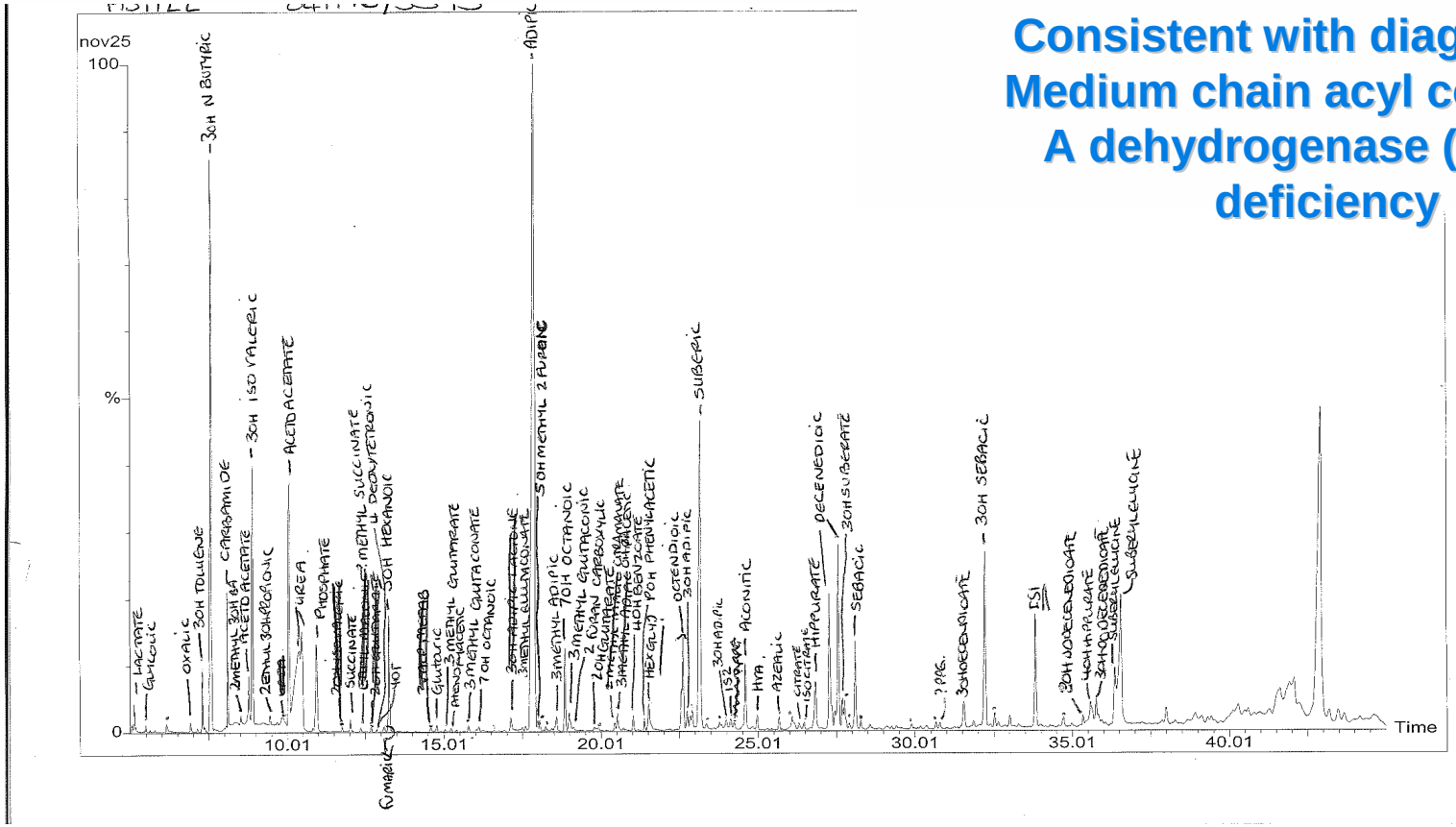
- **Samples must be taken at time of hypoglycaemia to allow accurate interpretation. Ratio can be used to determine further investigations.**



Patient in this case had a FFA/3OH-butyrate > 3

Organic acid analysis

- Organic acid analysis showed increased excretion of adipate, suberate, sebacate, 3-OH suberate, decendioic acid, suberylglycine, hexanoylglycine and phenylpropionylglycine…….



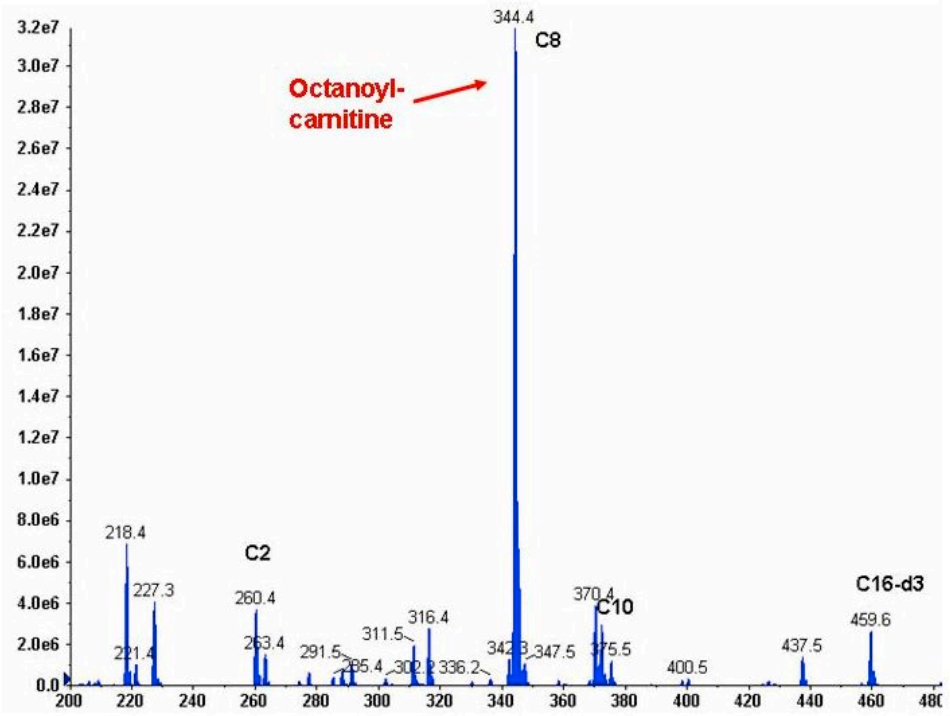
Consistent with diagnosis of Medium chain acyl coenzyme A dehydrogenase (MCAD) deficiency

Acylcarnitine analysis

- Initial (lithium heparin) acylcarnitine analysis showed low free carnitine (1.6 µmol/L, reference range 3.5-35). This means the sample was unsuitable for detecting raised octanoylcarnitine (C8) –a marker abnormality in MCADD.

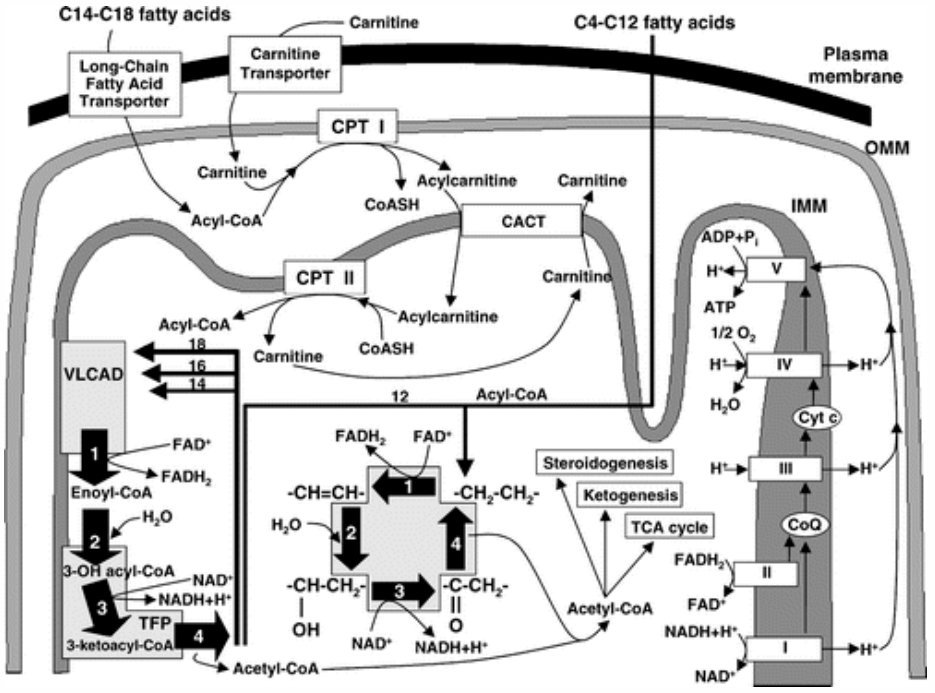
- Tandem-MS of the child's neonatal blood spot revealed a significantly increased C8 of 1.13 µmol/L (reference range < 0.3). A result strongly suggestive of MCAD

- DNA Mutation screening confirmed that patient was homozygous for the common K304E (985G-A) mutation confirming the diagnosis



What is MCAD deficiency

- Deficiency of medium chain acyl coenzyme A dehydrogenase enzyme results in inability to break down intermediate length fatty acids
- Fatty acids are unable to be metabolised beyond the 6-12 carbon stage
- There is an impaired ketogenic response to fasting
- This leads to hypoglycaemia due to a failure of gluconeogenesis



MCAD deficiency

- An incidence of 1 in 10 000 in live births, 1 in 80 are carriers
- Common symptoms; **hypoketotic hypoglycaemia**, vomiting, diarrhoea and lethargy
- Complications; hepatomegaly, breathing difficulties, seizures, coma, brain damage and sudden death
- Mutation K304E (985G-A) common in North-European Caucasians, which leads to reduced production of an unstable protein. Ethnic variability in MCAD mutations and prevalence.
- Most sensitive and specific markers for the disease are urinary hexanoylglycine in a hypoglycaemic episode by organic acid analysis and plasma C8 by Tandem-MS
- A high FFA/3-OH butyrate ratio (> 2) when hypoglycaemic and carnitine deficiency can also be suggestive of FAOD

MCAD deficiency treatment and outcomes

- The cornerstone of treatment is the avoidance of fasting
- Babies and children should not go without eating for longer than 6 hours
- Teenagers and adults have improved fasting tolerance (at least 12 hours) due to the increase in glycogen stores with age.
- Cornstarch is commonly used as it has increased levels of complex carbohydrate, resulting in a slower release of glucose.
- Carnitine supplementation
- Patients/parents are provided with emergency dietary regime
- Outcomes are good

Patient follow up

- The child has an older sibling, who was screened for MCADD and found to be unaffected
- Parents were counselled that any future children would have a 1 in 4 risk of being affected
- The patient is doing well, weight on 50th centile and height of the 91st centile
- No organomegaly
- Enjoys taking part in sports at school but has been advised to avoid endurance sports

Summary

- A child presented with a gastroenteritis with vomiting and diarrhoea.
- Since the child also had a defect in fatty acid oxidation the lack of carbohydrate intake and its loss lead to a profound hypoglycaemic episode explaining the acute neurological symptoms**.**
- The elevated ALT, CRP and ammonia were probably secondary to the initial infection and not primarily related to MCADD.
- The organic acid results were diagnostic of MCADD – it is important to collect samples prior to treatment as this may normalise results.
- The low plasma carnitine was secondary to the accumulation of acylcarnitines and possibly the poor food intake. A low plasma carnitine can mask fatty acid oxidation defects.
- Whilst the total plasma free fatty acids and D-3-hydroxybutyrate were not clearly abnormal the ratio of FFA/3-HB was abnormal.
- MCADD screening is now part of the UK Newborn Screening programme and all children are tested on a heelprick blood spot collected at 5-10 days of age