

Multiple acyl-CoA Dehydrogenase Deficiency: a rare cause of hypoglycaemia

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Introduction

Hypoglycaemia is a common problem that leads to referral to inpatient and outpatient Endocrinology services.

The differential diagnosis for hypoglycaemia is wide and successful diagnosis depends on thorough clinical history taking and examination to identify key features indicative of endocrine and non endocrine diagnoses.

We describe an unusual cause of hypoglycaemia caused by a late presentation of an in born error of metabolism: **Multiple acyl-CoA Dehydrogenase Deficiency (MADD)**.

Case

- We report the case of a 37-year-old woman with a 9-month history of intermittent and variable symptoms of anorexia, nausea & vomiting, weight loss, muscular weakness and pain in association with recurrent hypoglycaemic episodes.
- The patient had no significant past medical or family history of note and had not been prescribed any hypoglycaemia agents.
- The patient was admitted to hospital on several occasions with intermittent and ill explained symptoms before a diagnosis was achieved.

Investigations, management and follow up

The patient stated that she had experienced **intermittent episodes** of **muscular aches** with **generalised weakness** affecting her mobility and a history of significant **weight loss** as a result of **anorexia** with **nausea** and **vomiting**. The patient had been admitted to hospital on three previous occasions with symptoms as described and had made an improvement with supportive treatments. Case note review revealed **hypoglycaemia** as confirmed by low finger prick blood glucose readings, < 3 mmol/L, but otherwise there was extensive normal biochemical and radiological investigations. It was thought that the symptoms were psychological in nature and that the the low blood glucose readings were spurious.

The patient was readmitted for a fourth time several weeks after the third discharge from hospital with a **generalised weakness**, an inability to raise her head from chest, and further **hypoglycaemia**. Previously abated symptoms of **anorexia** with **nausea** and **vomiting** and **muscular aches** had returned worse than before. There was no clear relationship between symptoms and signs, hypoglycaemia and resolution of hypoglycaemia.

Investigations on re-admission to hospital revealed **hypoglycaemia** on two occasions with a formal lab glucose of 2.0 mmol/L and 3.2 mmol/L. HBA1C was 29 mmol/Mol. Serum creatine kinase was raised to greater than 1000 u/L, venous lactate was raised at 4 mmol/L and serum bicarbonate was 15 mmol/L. Liver transaminases were mildly raised but renal function was normal. On examination the patient had weakness of her limbs, had difficulty lifting her head up from her chest, and was tender to examination all over. An Endocrine opinion was sought with regards to a possible Insulinoma, however this was thought be unlikely given the clinical history on presentation, the feature of weight loss rather than expected weight gain and as "Whipple's triad" had never been met.

A **metabolic disorder** was suspected owing to the combination of intermittent and variable symptoms in association with hypoglycaemia, raised Creatine Kinase level, deranged liver function tests and **metabolic acidosis**. A **Urine organic acid profile** was performed and revealed **raised 2-hydroxyglutarate levels** suggestive of **Multiple Acyl-CoA Dehydrogenase Deficiency (MADD)**. The patient was commenced on treatment with oral **Riboflavin**, vitamin B2, and her symptoms improved as did the biochemical abnormalities. Subsequent genetic analysis revealed a **heterozygous EFTDH mutation** confirming the diagnosis.

Discussion

- **Multiple acyl-CoA dehydrogenation deficiency (MADD)** is a autosomal recessive disorder of fatty acid and amino acid oxidation.
- Mutations in **ETFA**, **ETFB** and **ETFDH** genes, which encode subunits of electron transfer flavoprotein and ETF-coenzyme Q oxidoreductase, can lead to dysfunction of either of these two flavoproteins and to compromised fatty acid oxidation.
- **MADD** is a clinically heterogeneous disorder ranging from a fatal neonatal presentation with **metabolic acidosis**, cardiomyopathy and liver disease, to a mild late onset disease with **intermittent metabolic decompensation**, **muscle weakness**, and **hypoglycaemia**.
- Treatment is supportive in nature though a riboflavin, vitamin b2, responsive variant has been identified. Almost all late onset cases are riboflavin responsive

Conclusion

- MADD is a rare cause of hypoglycaemia.
- Unexplained symptoms may develop over time and lead to an eventual diagnosis
- As Endocrinologists special consideration must be given to potential non endocrine and more unusual causes of hypoglycaemia.

References

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