Hypoglycaemia Precipitated By Protein Ingestion: The Hyperinsulinism/ Hyperammonaemia Syndrome

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INTRODUCTION

Hyperinsulinism-hyperammonia (HI/HA) syndrome

- Caused by activating mutations in the glutamate dehydrogenase gene GLUD1 (1).
- Leads to increased sensitivity to insulin release following (leucine containing) protein ingestion (1, 2) *(Figure 1)*
- Hallmarks -postprandial hypoglycaemia and asymptomatic persistant mild hyperammonemia (2).
- Associated with mild learning disability and seizures (3).
- Responds well to oral diazoxide therapy (2).

CASE HISTORY

Initial presentation at 9 months of age

- Hepatomegaly, hypoglycaemic seizures
- Liver biopsy suggestive of metabolic hepatopathy
- Managed as glycogen storage disease

At 5 years of age

- Intermittent hypoglycaemic seizures despite frequent feeds, corn starch
- Mid-afternoon lethargy, drowsiness, mild learning difficulty & obesity (Figure 2 a)
- Reduction in hepatomegaly

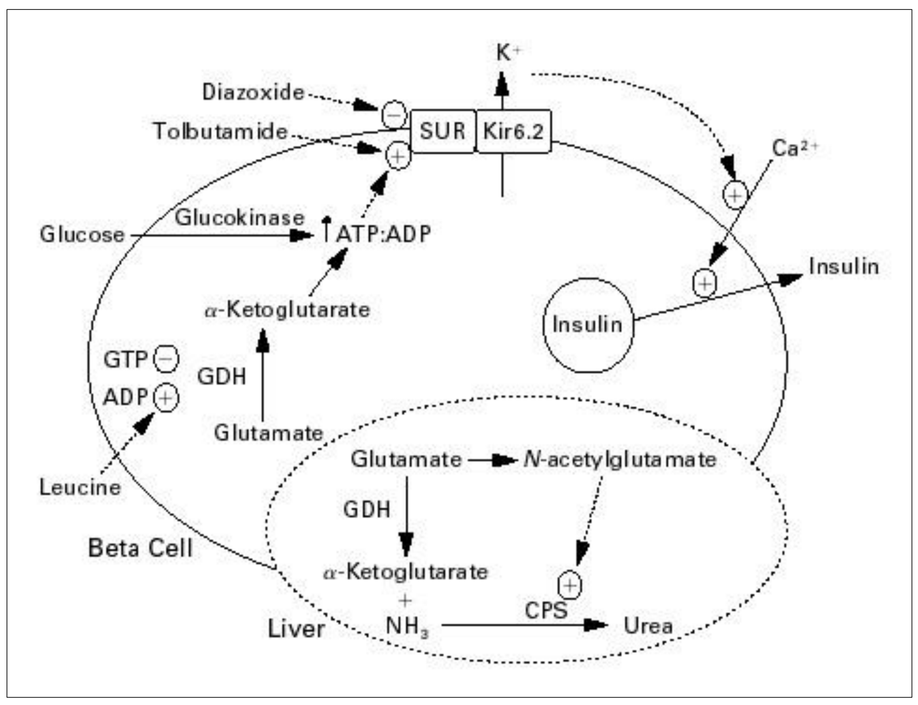

Figure 1. Glutamate Dehydrogenase (GDH) and regulation of insulin secretion and hepatic urea genesis [adapted from CA Stanley *et. al.* (1)]

Leucine indirectly stimulates insulin secretion by allosterically activating glutamate dehydrogenase (GDH) and increasing the oxidation of glutamate.

In the liver, glutamate governs the synthesis of N -acetylglutamate, an allosteric effector of carbamoyl-phosphate synthetase (CPS). Oxidation of glutamate by glutamate dehydrogenase also provides free ammonia.

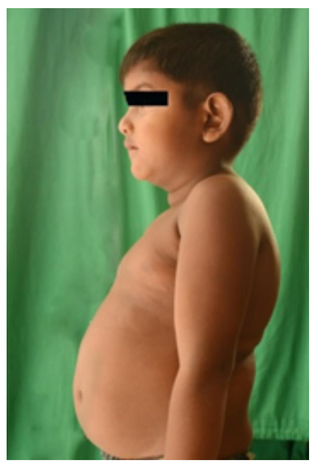

Figure 2 a

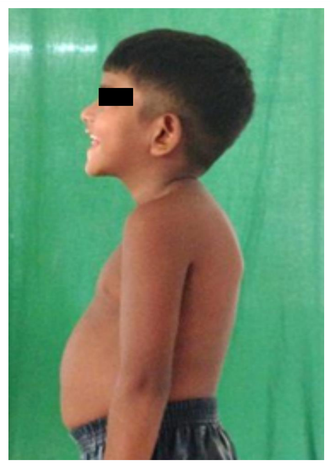

Figure 2 b

Figure 2- a) Child at 5 years of age with obesity , prior to commencing diazoxide treatment
b) Child 6 months after diagnosis, showing rapid resolution of obesity

EVALUATION AND MANAGEMENT

On re-evaluation in ward;

- Capillary blood glucose level monitoring 60-90 mg/dl
- Supervised fast tolerated for 18 hours without hypoglycaemia
- Hypoglycaemic seizure an hour after dinner (rice, dhal and egg)
- Detectable serum insulin on critical sample, and absent urine ketone bodies

HI/HA syndrome suspected

→Oral protein tolerance test performed (ingestion of protein 1.5 mg/kg) (4).

- Symptomatic hypoglycaemia within an hour of protein loading
- Hypoglycaemia corrected with IV glucagon
- Elevated serum ammonia

Management

- Oral diazoxide (5 mg/kg/day) in 2 divided doses
- Low protein diet (restricting leucine-rich foods such as chicken, fish, egg, dhal)

Follow up

- Resolution of lethargy, hypoglycaemia and seizures
- Rapid improvement in obesity over six months (Figure 2 b)

CONCLUSIONS

- Correct diagnosis and treatment of HI/HA syndrome led to resolution of hypoglycaemia, lethargy and seizures and rapid improvement in obesity in the child
- HI/HA can be biochemically confirmed and managed easily if suspected, emphasizing the importance of awareness of this entity
- Hepatomegaly, although not previously reported, does not exclude the diagnosis

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The authors have no potential conflicts of interest to declare

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