

A case of persistent hyperinsulinaemic hypoglycaemia of infancy (PHHI) successfully treated with diazoxide

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Introduction

Hyperinsulinism is a commoner cause of persistent or recurrent hypoglycaemia in infancy than one would expect^{1,2}. It is also a major cause of neurological damage and life long handicap due to the difficulties in management despite recent advances^{1,2}.

Case report

A 14 day old baby girl was transferred from an intensive care unit (ICU) of a local hospital to the ICU of Lady Ridgeway Hospital (LRH) with a history of recurrent refractory seizures since 20 hours of life. She was born to non-consanguineous healthy parents after an uncomplicated antenatal period, with a birth weight of 3,045g. She was non-asphyxiated and did not have risk factors for sepsis. However, she had obvious macrosomic features. Towards the end of the first day she developed lethargy, drowsiness, poor sucking and had a random blood sugar (RBS) of < 2mmol/L, while on full feeds. She was immediately put on antibiotics and dextrose drip after a septic screen. At 30 hours she started getting generalised seizures which were refractory to intravenous phenobarbitone. At 38 hours she developed prolonged apnoea and respiratory arrest needing ventilatory support. After weaning off from ventilation the baby was transferred to ICU LRH for further investigation.

By this time she was on a dextrose infusion 8–10mg/kg/hr. Serum electrolytes, renal and liver functions were within normal limits. Septic screen was also normal. Serum insulin and C-peptide levels on two occasions were very high (19.8miu/ml and 17.9miu/ml for insulin) despite an RBS <2.3mmol/L. Ketones were absent from urine. Plasma free fatty acid level was not done due to the unavailability of the facility. Ultrasound scan of the abdomen showed prominent pancreas but CT scan was normal.

She was started on octreotide infusion which cut down the concentration of dextrose needed to maintain normoglycaemia. Then oral diazoxide was started at a low dose and gradually increased to 12.5 mg 8 hourly until normoglycaemia was achieved without octreotide. Patient was sent home on that treatment and was stable for more than one month when tailing off of diazoxide was started. She was able to maintain normoglycaemia without diazoxide at 2 ½ months of age but unfortunately had mild cerebral atrophy at that time.

Discussion

Most patients with PHHI present in the neonatal period or infancy^{1,2}. 30–50% of patients were found to have abnormalities related to genes controlling SURI (sulfonylurea receptor 1) - ATP sensitive potassium (KATP) channel in β cell membrane³. Demonstration of high requirement of glucose (> 8–10 mg/kg/hr) to maintain RBS>2.3 mmol/L, is a main indicator for further investigations^{1,2}. Insulin concentration should be inappropriately high during documented hypoglycaemia with hypofattyacidaemia (<1.5mmol/l) hypoketonaemia (<2mmol/l) and inappropriate glycaemic response to glucagon injection⁴.

In 1999, European Network for Research into Hyperinsulinism has laid down a practical guide^{1,5} for management of PHHI which emphasises early referral to a tertiary centre and establishing the diagnosis. Objectives of management are: 1. Prevent hypoglycaemic brain damage and allow normal psychomotor development, 2. Establish normal feed volume, content and frequency for age of the child, 3. Ensure normal tolerance of fasting without developing hypoglycaemia.

Medical management includes initial resuscitation with high infusion rates of glucose via a central line with nasogastric feeds. Pharmacological agents can then be added to cut down the insulin secretions. Treatment of choice is oral drug therapy e.g. diazoxide 10-20 mg/kg/day, in 2-3 divided doses which activates kATP channels⁶. Fluid retention,

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hypertrichosis, hyperuricaemia and marrow suppression are reported side effects of this drug. Fluid retention can be combated with chlorothiazide which also has an effect on K channels.

Voltage dependent Ca channel activation can be blocked by nifedipine (0.25–2.5mg/kg/day) but long term efficacy and outcome are not yet established. Glucagon (1–10µg/kg/hour) which mobilises glycogen stores and octreotide (5–20 µg/kg/day) are second line drugs as they are available in injectable forms. The place for steroids is controversial.

Failure to respond to medical treatment after 4–6 weeks requires a surgical approach. Absolute indications for surgery are demonstration of focal hyperplasia of pancreas and glucose infusion dependency despite maximum doses of diazoxide, chlorothiazide, nifedipine, glucagon and octreotide.

Children who respond to diazoxide treatment should be maintained on their initial dose with repeated attempts to withdraw drug during the next few months. This should be done only in hospital.

The natural history of the disease is one of progressive glucose intolerance and clinical diabetes which might be the result of enhanced apoptosis in hyperinsulinaemic β cells.

References

1. Aynsley-Green A, Hussain K, Hall J, Saudubray J M, Nihoul-Fekepe C, De Lonlay-Debeney P, et al. Practical management of hyperinsulinism in infancy *Arch Dis Child Fetal Neonatal Ed* 2000; **82**: 98–107.
2. Soltesz G, Aynsley Green A. Hyperinsulinism in infancy and childhood. *Ergeb Inn Med Kinderheilkd* 1984; **51**: 115–202.
3. Aynsley Green A, Soltesz G, Jenkins P A. hyperinsulinaemic hypoglycaemia in infancy and childhood- a practical approach to diagnosis and treatment based on experience of 18 cases. *Acta Paediatr Hung* 1984; **25**: 319–32.
4. Aynsley Green A, Jenkins P A, Tronier B, Heding L G. Plasma proinsulin and c-peptide concentrations in children with hyperinsulinaemic hypoglycaemia. *Acta Paediatr Scand* 1984; **73**: 359–63.
5. Meissner T, Brune W, Mayapepak E. Persistent hyperinsulinaemic hypoglycaemia of infancy: therapy, clinical outcome and mutational analysis. *Eur J Pediatr* 1997; **156**: 754–7
6. Dunne M J, Peterson O H. Potassium selective ion channels in insulin secreting cells: physiology, pharmacology and their roll in stimulus secretion coupling. *Biochem Biophys Acta* 1991, **1071**: 67–82