HYPERINSULINEMIC HYPOGLYCEMIA IN A CHILD WITH PEROXISOMAL BIOGENESIS DISORDER DUE TO A NOVEL PEX1 MUTATION

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BACKGROUND

- Peroxisomal biogenesis disorders are autosomal recessive disorders characterized by defective biosynthesis, assembly and function
- The primary cause of these disorders is due to mutations in PEX gene.
- PBDs are classified into two types: PBD- Zellweger spectrum disorder (PBD-ZSD) and rhizomelic chondrodysplasia puncatata type 1
- Hypoglycaemia is not reported in peroxisomal disorders. Although peroxisomes play a role in very long chain fatty acid oxidation, the main pathway of fatty acid oxidation (FAO) occurs in mitochondria.
- Hypoglycaemia occurring in a child with PBD needs thorough work-up to find the etiology

CASE

- A 7 month old boy was referred with the complaints of irritability and excessive cry.
- He was known to have multiple problems in the form of bilateral sensorineural hearing loss, global developmental delay, hypotonia, visual impairment and gastroesophageal reflux.
- No family history of diabetes mellitus or hypoglycaemia was reported.
- He was born at 41 weeks of gestation with a birth weight of 3.7 kg (0.48 SDS).
- On examination hepatomegaly, dysmorphic features including asymmetry of nasal cleft, leg crease, sacral dimple, metatarusus adductus and right undescended testis were noted.
- Investigations revealed deranged liver function [AST- 1576 Iu/L (12-41), ALT- 918 iu/L (80-36), GGT- 163 Iu/L (0-50), Total Protein- 67 g/L (67-92), Albumin- 40 g/L (38-58), PT-15.3 sec (9.1-11.8), INR- 1.48, APTT- 27.6 sec (22.8-34.7)], normal serum electrolytes and blood gas analysis.
- The child started to have repeated episodes of Hypoglycaemia requiring high glucose infusion rate (GIR) of 10.6 mg/kg/min.
- Critical sample during hypoglycaemic episode revealed a blood glucose of 2.5 mmol/L (>2.6 mmol/L), Insulin of 18 mIU/mL C-peptide of 116 pmol/L and beta hydroxyl butyrate (<100 µmol/L) and free fatty acid undetectable (FFA) (<275 µmol/L) were undetectable suggestive of HH.
- The child was started on intravenous glucagon and high concentration intravenous dextrose (GIR 10.6 mg/kg/min) to which he responded well. Echocardiogram showed a structurally and functionally normal heart study.
- The cortisol was 364 nmol/L during hypoglycaemia. Standard short synacthen test revealed a baseline cortisol of 147nmol/L and a suboptimal peak of 214nmol/L suggesting adrenal insufficiency.

CASE

- The constellation of features of sensorineural hearing loss, hepatomegaly, visual impairment, hypotonia, developmental delay, liver dysfunction and adrenal insufficiency made peroxisomal disorders as a likely diagnosis.
- The ratio of very long chain fatty acid C24/C22 was 1.76µmol/L (0.44-0.97) and Very Long chain Fatty acid C26/C22 ratio was 0.339µmol/L (0.005-0.03) indicative of PBD-ZWS or isolated beta oxidation of fatty acid defect.
- Urinary bile analysis showing elevated taurine 548µMl/mMCr (9-123) with notable presence of taurotrihydrocholestanoate, taurotetrahydrocholestanoate with much increased ratio of taurotetrahydrocholestanoate/ taurotrihydrocholestanoate which was suggestive of PBD-ZWS.
- The child was commenced on diazoxide (3 mcg/kg/day) and chlorothiazide (6 mg/kg/day). Dose of diazoxide was increased to maintain blood glucose >3.5mmol/L to a maximum of 15 mg/kg/day and GIR was tapered and intravenous fluids were discontinued.
- Gradually the blood glucose improved but his oral intake was sub-optimal hence nasogastric feeds were commenced and subsequently a percutaneous endoscopic gastrostomy was inserted.
- The child tolerated diazoxide well without any complications. Diazoxide was slowly weaned and stopped after total treatment duration of 40 days.
- Genetic analysis for PBD-ZWS showed two heterozygous mutations in PEX1 [c.2097dupTp.(Ile700TyrfsTer42) and c.1838G>A p.(Cys613Tyr)] with the first one known to be a common pathogenic variant to cause PBDs in both compound heterozygous and homozygous states and the later was proposed to be a pathogenic variant.
- The cause of hyperinsulinism was not identified on genetic analysis of known HH genes (ABCC8, KCNJ11, and HNF4A1).

CONCLUSION

- Hypoglycaemia in a child with peroxisomal disorder needs a thorough approach.
- Although rare, HH should be considered.
- Treatment with diazoxide could help in the management of hypoglycaemia

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