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Two Siblings with Tyrosinaemia Type 1 and Transient Hyperinsulinaemic Hypoglycaemia

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INTRODUCTION

TYROSINEMIA
A RARE GENETIC
METABOLIC DISORDER

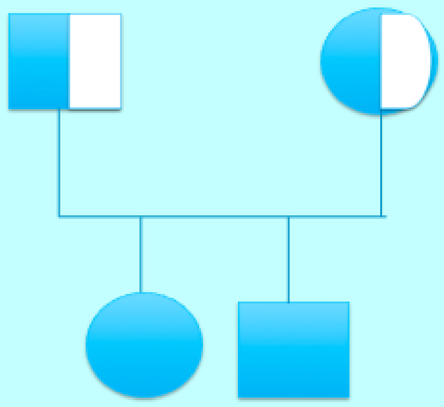
•A rare autosomal recessively inherited disorder of tyrosine metabolism leading to accumulation of tyrosine and its metabolites in liver, kidney and central nervous system

•Has a broad spectrum of clinical manifestations

•Hypoglycaemia is common, especially in the acute phase of the disease due to liver failure and reduced hepatic clearance of insulin. However confirmed cases of hyperinsulinaemic hypoglycaemia have also been recently described.

CASE

- The proband was a female child diagnosed with TT1 following an elevated phenylalanine on newborn screening and liver failure.
- Neonatal hypoglycaemia.
- Hypoglycaemia screen confirmed the diagnosis of hyperinsulinaemic hypoglycaemia which was well controlled on combination of diazoxide and chlorothiazide.
- Her treatment was discontinued after 8 months with normal blood glucose (BG) control and appropriate fasting duration since then.



- Both siblings were found to be homozygous for pathogenic variant c. 192G>Tp.
- (Gln64His) in fumarylacetoacetate hydrolase (FAH) gene which they inherited from their consanguineous parents who were heterozygous carriers of the same mutation

- Her brother was screened and diagnosed with TT1 at birth due to positive family history.
- Neonatal hypoglycaemia.
- Diagnostic workup revealed detectable insulin at the time of hypoglycaemia and inability to mobilise ketones and fatty acids confirming the diagnosis of hyperinsulinaemic hypoglycaemia.
- Therefore, he was commenced on diazoxide and chlorothiazide which normalised his BG.
- His treatment was discontinued after 6 months with age appropriate fast tolerance and no further hypoglycaemia off medication.

CONCLUSIONS

We describe two siblings with TT1 and acute liver dysfunction who had transient hyperinsulinaemic hypoglycaemia in the neonatal period. Both siblings were successfully treated with diazoxide (3mg/kg/day) and chlorothiazide (7mg/kg/day) and treatment was gradually withdrawn after 8 and 6 months, respectively.

Although histological abnormalities of the pancreas including beta cell hyperplasia are well documented, the exact mechanism of excessive insulin secretion in TT1 is not well understood. It may be related to the accumulation of toxic metabolites in the target organs including pancreas. Therefore, in patients with TT1 and persistent hypoglycaemia, it is important to exclude hyperinsulinism which is usually transient and can be successfully treated with diazoxide and chlorothiazide. Further studies are required to determine which factors contribute to excessive insulin secretion in patients with TT1

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58ESPE P2-143
Fetal, neonatal endocrinology and metabolism (to include hypoglycaemia)
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Poster presented at: ESPE 2018 VIENNA
PosterSessionOnline.com