Diazoxide-responsive hyperinsulinaemic hypoglycaemia in tyrosinaemia type 1

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Summary

Tyrosinaemia type 1 (TT1) is a rare inherited disorder of amino acid metabolism typically presenting with liver failure and renal tubular dysfunction. We describe three individuals with TT1 and transient hyperinsulinaemic hypoglycaemia (HH). Two siblings with TT1 and acute liver dysfunction were diagnosed with hyperinsulinaemic hypoglycaemia in the neonatal period. Both siblings were successfully treated with diazoxide/chlorthiazide and treatment was gradually weaned and stopped after 8 and 6 months of age respectively. The third patient presented with a neonatal liver failure with mild cholestasis, coagulopathy, fundus haemorrhages, vitamin A and E deficiency and hyperinsulinaemic hypoglycaemia. He maintained euglycaemia on high dose diazoxide (5–12 mg/kg/day) but developed pulmonary hypertension at 12 weeks of age. After discontinuation of diazoxide, he continued maintaining his blood glucose (BG) within the normal range. 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 beyond the recovery of the acute liver failure, 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.

Learning points:

- Every child with TT1 should be monitored for signs and symptoms of hypoglycaemia and screened for HH at the time of real hypoglycaemia.
- If hypoglycaemic episodes persist even after improvement of liver function, hyperinsulinism should be suspected.
- Treatment with diazoxide is effective, however, children need to be monitored closely for possible side effects.
- The pathophysiological mechanism of hyperinsulinism in children with TT1 is not elucidated yet and further studies are required to determine which factors contribute to excessive insulin secretion in patients with TT1.

Background

Tyrosinaemia type 1 (TT1) is a rare autosomal recessively inherited metabolic disorder characterised by disruption of the last step of tyrosine metabolism. The resulting accumulation of toxic metabolites such as maleylacetoacetate, fumarylacetoacetate and succinylacetone leads to progressive liver disease, renal tubular dysfunction and porphyria-like crises (1). Hypoglycaemia is not uncommon, especially

in the acute form of TT1, and could contribute to neurodevelopmental impairment observed later in life. In regard to aetiopathological mechanisms, hypoglycaemia was described to be associated with acute liver failure and reduced hepatic clearance of insulin (2). So far, only a few patients have been reported with hyperinsulinaemic hypoglycaemia (HH) persisting beyond the recovery of the acute liver failure (3). Here we describe three cases of TT1 with confirmed transient HH persisting for several months following the acute liver failure recovery.

Case reports

Patients' clinical and biochemical findings are summarised in Table 1.

Case 1

The first patient was a female child born at term to consanguineous parents. She was diagnosed with elevated phenylalanine in newborn screening and liver failure, which triggered further metabolic investigations that revealed high plasma tyrosine levels indicative of TT1. Analysis of urine organic acids revealed elevated 4-hydroxyphenyllactate, 4-hydroxyphenylpyruvate and succinylacetone, consistent with TT1. She was commenced on a tyrosine- and phenylalanine-restricted diet and Nitisinone (NTBC, 2-(2-nitro4-trifluoromethylbenzoyl)-1,3-cyclohexanedione) (1) which was well tolerated. Genetic testing has shown that the patient was homozygous for the pathogenic variant c.192G>T p.(Gln64His). Analysis of parental samples confirmed that both parents were heterozygous for the mutation. She was also found to be hypoglycaemic on Day 5 of her life and required intravenous glucose with a glucose infusion rate of up to 9 mg/kg/min. Hypoglycaemia screen revealed detectable insulin and inability to mobilise ketones and fatty acids confirming the diagnosis of HH (Table 1). Therefore she was commenced on diazoxide (3 mg/kg/day) and chlorothiazide (7 mg/kg/day) on Day 10 of life and responded well. She was discharged home after a couple of weeks, fasting up to 6 h without supplemental carbohydrates and with normal blood glucose (BG) at the end of the fast. Hypoglycaemia persisted even after recovery of liver function. She continued to outgrow diazoxide and after 8 months age, diazoxide was stopped and she was able to fast for 12 h with normal BG at the end of the fast.

Table 1 Clinical and biochemical features of three subjects with TT1 and transient HI.

	Patient 1	Patient 2	Patient 3
Birth weight (grams)	2700 (−2.11 SDS)	2280 (−1.5 SDS)	2530 (−1.03 SDS)
Gestation (weeks)	Term	36	36 + 4
Diagnosis of TT1 (days)			
Neonatal screening	Yes (Day 5)	Yes (Day 5)	Yes (Day 5)
Urine organic acid analysis (succinylacetone)	Yes	Yes	Yes
Genetic confirmation	Yes (Day 50)	Yes (Day 28)	Yes (Day 78)
Genotype	Homozygous for pathogenic variant c.192G>Tp.(Gln64His) in FAH-gene	Homozygous for pathogenic variant c.192G>Tp.(Gln64His) in FAH-gene	Homozygous for pathogenic variant c.1062+5G>A (p.?) in FAH-gene
Onset of initial hypoglycaemia	Day 5	Day 14	Day 1 (14 hours of age)
Hypoglycaemia screen			
Lab glucose (3.5–5.5 mmol/L)	2.1 mmol/L (38 mg/dL)	1.9 mmol/L (34 mg/dL)	2.5 mmol/L (45 mg/dL)
Insulin (<2 mU/L)	3.8 mU/L	4.6 mU/L	31.3 mU/L
C-peptide (pmol/L)	610 pmol/L	348 pmol/L	Not done
Non-esterified fatty acids (1–2mmol/L)	<0.05 mmol/L	0.05 mmol/L	Not done
-Hydroxybutyra (1–2mmol/L)	0.22 mmol/L	0.05 mmol/L	Not done
Lactate (0.7–2.1 mmol/L)	2.4 mmol/L	1.1 mmol/L	1.62 mmol/L
HI treatment initiated	Day 10	Day 21	Day 12
Diazoxide dose	3 mg/kg/day	3 mg/kg/day	5–12 mg/kg/day
Diazoxide duration	8 months	6 months	3 months
Diuretics	Chlorothiazide (7 mg/kg/day in two divided doses).	Chlorothiazide (7 mg/kg/day in two divided doses).	-
Diuretics length	8 months	6 months	-
Pulmonary hypertension	No	No	Yes (on Day 84)
Fasting tolerance	12 hours off diazoxide at the age of 8 months	12 hours off diazoxide at the age of 6 months	7 hours off diazoxide at the age of 13 weeks

Case 2

The second patient was the brother of Case 1. He was born at 36 weeks of gestation and was screened for TT1 at 24 h after birth due to a positive family history of TT1. Biochemical parameters were suggestive of TT1 and genetic analysis confirmed the presence of the same homozygous mutation which was identified in his sister. He was treated with a tyrosine- and phenylalanine-restricted diet and NTBC since the first week of his life. He also had episodes of hypoglycaemia in the neonatal period, which initially were related to liver derangement due to TT1. However, despite improvement in his liver function, he was not able to maintain his BG. Hypoglycaemia screen confirmed the diagnosis of HH (Table 1) which was well controlled on the combination of diazoxide (3 mg/kg/day) and chlorothiazide (7 mg/kg/day), which led to age-appropriate fasting tolerance without any supplemental carbohydrates. His treatment was discontinued after 6 months when he tolerated a 12 h fast, off diazoxide.

Case 3

The third patient was male, born in Germany at 36+4 weeks of gestation to consanguineous parents of Syrian origin. Family history revealed that an older sibling passed away at the age of 11 years due to unknown liver disease in Syria and another sibling has been diagnosed with prune belly syndrome. Our patient had a complicated neonatal course with: (i) suspected sepsis requiring antibiotics with negative blood cultures and inflammatory markers, (ii) severe coagulopathy managed with repeated fresh frozen plasma (FFP), antithrombin III, vitamin K and platelet transfusions, (iii) cholestasis and conjugated hyperbilirubinemia, (iv) recurrent hypoglycaemia from as early as 14 hours of life. Initially, he required intravenous glucose with a glucose infusion rate of up to 12.5 mg/kg/min to maintain euglycaemia. Hypoglycaemia screen revealed the presence of insulin confirming the diagnosis of HH (Table 1). Therefore he was commenced on diazoxide initially at 5 mg/kg/day, which gradually was increased up to 12 mg/kg/day in order to stabilise his BG.

Tyrosinaemia type I was suspected early due to high tyrosine (180 μmol/L) and succinylacetone (6.99 μmol/L) levels on neonatal screening. Genetic testing confirmed the diagnosis and he was found to be homozygous for the pathogenic variant c.1062+5G>A in the fumarylacetoacetate hydrolase (FAH) gene. Hence, he was commenced on a low tyrosine/phenylalanine diet and NTBC, with no side effects and was discharged

home on the above treatment along with diazoxide. At 12 weeks of age, he was readmitted with signs of pulmonary hypertension requiring continuous positive airway pressure (CPAP), sildenafil and furosemide. Diazoxide was immediately discontinued as the perceived cause for his pulmonary hypertension (4). Following discontinuation of diazoxide his BG remained stable. A week later he tolerated a 7 h-fast off diazoxide. Currently, at the age of 9 months he remains euglycaemic off diazoxide and with no signs of pulmonary hypertension. Treatment with sildenafil was discontinued and he is currently only on Lisinopril 0.027 mg/kg/day and NTBC.

Discussion

We describe three patients with TT1 and HH. All patients presented with liver failure in their first days of life. Biochemical and genetic testing confirmed the diagnosis in all patients. Besides the typical TT1 associated problems all patients repeatedly presented with episodes of hypoglycaemia persisting even after liver function improved. Detectable insulin levels at the time of real hypoglycaemia confirmed the diagnosis of HH.

Hypoglycaemia in children with TT1 has already been described in early reports of tyrosinaemia. In 1967 Perry *et al.* described three patients with TT1 who suffered from hypoglycaemia (5). Histological analysis of the pancreas in children with tyrosinaemia revealed marked hypertrophy and increase in the number of the islets of Langerhans (5, 6). However, these histological abnormalities in the pancreas are not consistently seen in patients with TT1 (7). On the basis of laboratory findings and clinical observations of three patients with tyrosinaemia, Sass-Kortsak *et al.* suggested that hypoglycaemia may occur due to a secondary impairment of gluconeogenesis and insufficient stores of liver glycogen (8). Baumann *et al.* (3) suspected that tyrosinaemia-specific metabolites could affect intracellular ATP homeostasis in beta cells, inducing inappropriate insulin secretion similar to that caused by glucose influx. However, the pathomechanism of hyperinsulinism in children with TT1 has not been elucidated yet, and it remains unclear why only a small number of patients with TT1 suffer from HH.

Diazoxide, the first line drug for the treatment of congenital hyperinsulinism (9), was started in all patients and led to euglycaemia; however, the required dose was quite variable between 3 and 12 mg/kg/day. Unfortunately, patient 3 developed pulmonary hypertension at 3 months of age. This might be related to the fact that he was treated with a fairly high dose

of diazoxide without concomitant diuretic therapy. This severe side effect is seen in approximately 2.4% of all children treated with diazoxide (9). Treatment with diazoxide was discontinued and he remained euglycaemic since then. Responsiveness to diazoxide in children with TT1 and HH was also described in three patients reported by Baumann *et al.* in 2005 (3). As opposed to our patients who were treated with diazoxide for 3–8 months the patients reported by Baumann *et al.* needed treatment for 9–34 months (3), however, remission might also have occurred earlier as diazoxide withdrawal was tried quite late. The age of onset of hypoglycaemia differs widely between the patients. As opposed to our three patients, who were diagnosed with their first hypoglycaemic episodes between 1 and 14 days of life, the three patients reported by Baumann *et al.* were diagnosed with their first hypoglycaemic episode later, between 21 and 84 days of life (3). It remains unclear if these children had undiagnosed hypoglycaemic episodes earlier because symptoms of hypoglycaemia can be subtle in neonates and might be easily overseen. It is well known that adverse neurodevelopment is reported in 26–48% of patients with recurrent hyperinsulinaemic hypoglycaemia (10). Children with TT1 have an increased risk for neurocognitive problems, including a lower IQ and abnormal motor skills (11), which should not be aggravated by a delayed diagnosis or inadequate treatment of HH, especially because treatment with diazoxide is effective in children with TT1 and HH.

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