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Hyperinsulinism in tyrosinaemia type I

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Summary: Tyrosinaemia type I (TT I) (McKusick 276700) is a heterogeneous disorder with a broad spectrum of clinical phenotypes. Although histological abnormalities of the pancreas are well recognized, there are only incidental reports of pancreatic dysfunction manifested as insulin-dependent diabetes mellitus. We report three subjects with TT I and acute liver dysfunction who had hyperinsulinism in early infancy. Hypoglycaemia persisted despite dietary treatment and one patient had inadequate lipolysis at the time of hypoglycaemia. All three patients were successfully treated with diazoxide (10 mg/kg per day) and chlorthiazide (35 mg/kg per day) and treatment was gradually withdrawn after 9, 13 and 34 months, respectively. The mechanism of pancreatic dysfunction in TT I is unknown but may be related to the toxic metabolites that accumulate in this condition. We conclude that hyperinsulinism is not a rare complication in TT I. In patients with persistent hypoglycaemia, C-peptide should always be measured. Treatment with diazoxide and chlorthiazide is highly effective, appears to be safe, and does not need to be continued lifelong.

Tyrosinaemia type I (TT I) (McKusick 276700) is a heterogeneous disorder with a broad spectrum of clinical presentation ranging from acute liver failure to the incidental finding of hepatomegaly and rickets (Holme and Lindstedt 1998; Mohan et al 1999). Hypoglycaemia is common in the acute form of TT I and can contribute to the neurological deficits observed later in the chronic course of the disorder (Meissner and Mayatepek 2002). Although histological abnormalities of the pancreas are well recognized (Larochelle et al 1973; Perry 1967) hypoglycaemia has traditionally been attributed to the severity of hepatic dysfunction (Mitchell et al 2001; Sass-Kortsak et al 1967). Among our 25 patients who presented with acute liver disease in infancy, three of these children also had hypoglycaemia (blood glucose level <2.6 mmol/L) and inappropriately raised insulin or C-peptide levels, thus fulfilling diagnostic criteria of hyperinsulinism (Aynsley-Green et al 2000).

SUBJECTS

A summary of patient data is shown in Table 1. Two children (patients 1 and 2) presented with clinical signs of acute liver dysfunction. The third child was diagnosed, as a consequence of the PKU screening programme, by the finding of raised tyrosine at 6 days of age. The child was then found to have significant liver disease. The diagnosis of TT I was confirmed in all children with low FAH activity in skin fibroblasts. Two patients (patients 2 and 3) were started on NTBC treatment shortly after the diagnosis of TT I was made.

In one hypoglycaemic child (patient 3), hyperinsulinism was confirmed by an inappropriately elevated serum C-peptide level while insulin levels appeared to be adequately suppressed. One child (patient I) had inappropriate suppression of lipolysis when hypoglycaemia was evident. This is in keeping with the current consensus on the diagnostic criteria for hyperinsulinism (Aynsley-Green et al 2000).

Imaging of the pancreas (ultrasound, CT) was normal in all three children, with no focal abnormality detected. In all three patients, hypoglycaemia persisted despite intensive dietary treatment, even leading to macrosomia in one child. This child (patient 1), born with a weight of 4.15 kg (97th centile), presented with mild to moderate liver dysfunction and was diagnosed to have TT I on day 54. NTBC treatment was not yet available and she was started on a Phe/Tyr-reduced diet. The liver

Table 1 Clinical and biochemical features of three patients with hyperinsulinism secondary to TT I[a]

		Patient 1	*Patient 2*	*Patient 3*
Birthweight (kg)		4.1	3.5	2.6
Diagnosis of TT I (days)		54	68	44
Laboratory investigations at time of diagnosis:				
INR		2.1	2.4	4.9
α-Fetoprotein (kU/L)		164 125	148 975	18 180
Onset of symptomatic hypoglycaemia (days)		84	63	21
Laboratory investigations at onset of hypoglycaemia:				
Simultaneous investigations:	*Normal values*			
Glucose (mmol/L)	(>2.2)	0.4	1.9	1.2
Insulin (pmol/L)	(<50)	326	111	42
C-peptide (pmol/L)	(<200)	–	545	451
Free fatty acids (mmol/L)	(0.1–0.6)	0.6	–	–
3-Hydroxybutyrate (mmol/L)	(0.0–0.3)	0.5	–	–
INR		1.6	–	4.9
α-Fetoprotein (kU/L)		140 895	–	18 180
Creatinine (μmol/L)		30	24	27
NTBC treatment commenced (days)		362	74	52
Length of drug treatment for hyperinsulinism (months) (diazoxide 10 mg/kg per day and chlorthiazide 35 mg/kg per day)		13	34	9

[a] All three patients were born at full term of consanguineous parents after normal pregnancy and by normal vaginal delivery

dysfunction improved, but at around 11 weeks of age she developed clinical evidence of hypoglycaemia. Despite dietetic intervention, hypoglycaemia persisted and medical treatment for hyperinsulinism was initiated. From then on her weight increased to 9.4 kg (1.5 kg > 97th centile) at the age of 4 months has not normalized since. Patients 2 and 3 developed hypoglycaemia before the diagnosis of TT I was established. Both children were started on dietary treatment when TT I was diagnosed. Liver function tests or specific laboratory investigations at the time of hypoglycaemia were either not done or were unchanged from the values when TT I was diagnosed.

Following the introduction of diazoxide (10 mg/kg per day) and chlorthiazide (35 mg/kg per day), all patients responded with rapid normalization of blood glucose levels. No significant side-effects were noted other than occasional vomiting, which was managed by continuous overnight feeds. None of the patients showed detectable changes of blood pressure or heart rate, nor did they develop bone marrow suppression. None of the patients required further surgical intervention such as partial pancreatectomy. After a gradual withdrawal of the drug treatment over several months, all three patients retained normal fasting tolerance. This was confirmed by an 8-hour fasting test. Among the three patients described, only the child in whom NTBC treatment was started late developed macrosomia as a sign of hyperinsulinism. Conversely, patient 2 with early NTBC treatment required a longer course of treatment with diazoxide and chlorthiazide.

DISCUSSION

Persistent hypoglycaemia is a common clinical feature accompanying the acute manifestation of TT I. To date this has been attributed to poor hepatic function leading to impaired glucose homeostasis or/and reduced hepatic clearance of insulin. Insulin secretion can be estimated from C-peptide concentrations and clearance (Faber et al 1978; Fiaccadori et al 1991). C-peptide is produced in equimolar proportion to insulin by cleavage from proinsulin. In contrast to insulin, which is metabolized by the liver, serum C-peptide is almost entirely excreted by the kidneys. Normal renal function in all three patients' data therefore confirms an inappropriately raised insulin secretion from pancreatic β-cells (rather then impaired insulin clearance). In one patient, following rapid resuscitation with glucose infusion, blood glucose levels had normalized and the hyperinsulinism could only be confirmed by raised C-peptide. Because of the shorter half-life of insulin compared to C-peptide, this constellation of results can be found in patients in whom blood glucose levels normalized following rescusitation and laboratory investigations were slightly delayed (Faber et al 1978). The results further support the hypothesis that impaired hepatic insulin clearance is not the determining factor for elevated insulin levels in this group of patients. In one other patient we were able to measure functional effects of hyperinsulinism. In this hypoglycaemic patient, lipolysis was inappropriately suppressed by the elevated insulin levels.

A therapeutic algorithm for children with hyperinsulinism has been suggested by the European network for research into hyperinsulinism (Aynsley-Green et al 2000). The appropriate first line treatment is a combination therapy of diazoxide and

chlorthiazide, followed if necessary by the addition of nifedipine (Eichmann et al 1999). Physiological insulin exocytosis from β-cells is dependent on cell membrane depolarization. Diazoxide inhibits membrane depolarization, and thus insulin secretion, by opening ATP-dependent K-channels (SURI, Kir6.2) that had been closed following glucose influx into the β-cell (Kane et al 1996).

Only half of all children with congenital hyperinsulinism of infancy can be diagnosed with a specific genetic defect (Fournet and Junien 2003); the majority of these have an underlying fixed blockage of the K-channel as described above. Consequently, their response to treatment with diazoxide is generally poor (de Lonlay et al 2002). The immediate response in our patients may be based on a defect higher in the cascade leading to insulin release. High intracellular glucose increases the ATP/ADP ratio, which is the appropriate stimulus for closure of the K-channel (Meissner and Mayatepek 2002). We suspect that the toxic metabolites accumulating in TT I may have an effect on this cellular energy balance, mimicking the presence of glucose and therefore leading to inappropriate insulin secretion.

The same toxic metabolites lead to continuous hepatic repair and the generation of nodules in the liver. The activation of hepatic stem cells under these circumstances has been proposed (Vassilopoulos et al 2003; Zhang et al 2003). These pluripotent cells belong to a common stem cell compartment (Baumann et al 1999) that is shared by liver and pancreas and that may give rise to increased numbers of β-cells as recently documented *in vitro* (Yang et al 2002) and *in vivo* (Sumazaki et al 2004). The typically grossly increased α-fetoprotein in these patients can be regarded as a progenitor cell marker and provides further evidence of significant activation of the stem cell compartment.

The role of NTBC in the disappearance of hyperinsulinism in these patients is unclear. NTBC results in a rapid, dramatic and sustained suppression of toxic intermediate metabolites in TT1 I (Holme and Lindstedt 1998). It is likely that this contributes to the clinical improvement we have observed. In two of our cases the hypoglycaemia persisted after the initial introduction of NTBC and in the first case recovery occurred before the availability of NTBC, implying that diazoxide/chlorthiazide treatment alone is sufficient for immediate reversal of hyperinsulinism in TT I. However, it appears likely that the long-term reduction of toxins subsequent to NTBC therapy terminates the underlying pancreatic pathology, which eventually allows discontinuation of the diazoxide/chlorthiazide treatment.

In summary, we suggest that the toxic metabolites in TT I may lead to a combination of islet cell hyperplasia and also interfere with the normal glucose/insulin homeostasis to produce hyperinsulinaemic hypoglycaemia. However, it still needs to be determined why TT I presents with such a broad spectrum of clinical phenotypes—or in our case why not all patients presenting with decompensated TT I develop hypoglycaemia. It seems possible that similar to other, non-TT I, patients hyperinsulinism of early infancy is only the first manifestation of disturbed pancreatic function and that with increasing survival of these patients insulin-dependent diabetes mellitus may become more frequent. The effect of the toxic tyrosine metabolites not only on the liver but also on the pancreas remains an interesting subject in clinical research and may reveal further insight into normal pancreatic growth and repair.

CONCLUSION

Hyperinsulinism is not a rare complication in TT I. In suspected cases C-peptide should always be measured. Treatment with diazoxide and chlorthiazide is highly effective, appears to be safe, and does not need to be continued lifelong.

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