Eur J Pediatr (2004) 163: 38–41
DOI 10.1007/s00431-003-1328-2

ORIGINAL PAPER

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Severe transient hyperinsulinaemic hypoglycaemia: two neonates without predisposing factors and a review of the literature

Received: 18 June 2003 / Accepted: 17 September 2003 / Published online: 29 October 2003

Abstract We report on transient hyperinsulinism (HI), presenting as severe congenital HI, in two neonates born without intrauterine growth restriction, maternal diabetes, perinatal asphyxia or Rhesus/platelet isoimmunisation. The neonates developed early (< 6 h of life), symptomatic, non-ketotic hypoglycaemia (0–0.66 mmol/l), associated with elevated insulin levels (40–200 mU/l), and required high glucose infusion rates (22–24 mg/kg per min) to maintain normoglycaemia. However, both babies were diazoxide-sensitive and did not require glucose infusions beyond 2 weeks of life. Neither neonate had elevated serum ammonia levels or evidence of a metabolic disorder. *Conclusion:* Transient hyperinsulinism can occur in newborns delivered uneventfully without significant perinatal complications. The unusual sensitivity to medical treatment in these cases of neonatal-onset hyperinsulinaemic hypoglycaemia underscores the importance of careful medical management of severe congenital hyperinsulinism. Careful consideration of the indication and if necessary, timing and extent of pancreatectomy is required, while maintaining euglycaemia to protect the developing brain.

Keywords Congenital hyperinsulinism · Diazoxide · Hypoglycaemia · Neonates · Transient hyperinsulinism

Abbreviations *AGA* appropriate for gestational age · *BGL* blood glucose level · *BWS* Beckwith-Wiedemann syndrome · *HI* hyperinsulinism · *HI/HA* hyperinsulinism/hyperammonaemia · *IUGR* intrauterine growth restriction · *PHHI* persistent hyperinsulinaemic hypoglycaemia of infancy · *SGA* small for gestational age · *SUR* sulphonylurea receptor · *TNHI* transient neonatal hyperinsulinism · *UVC* umbilical venous catheter

Introduction

Neonatal-onset persistent hyperinsulinaemic hypoglycaemia of infancy (PHHI) is a form of congenital hyperinsulinism (HI) which is usually severe, unlikely to be diazoxide sensitive [8, 20,24] and requires pancreatectomy in the majority of cases [12]. It is possible, however, that hyperinsulinaemic hypoglycaemia in neonates will resolve completely and spontaneously [8,25], a condition known as transient HI.

Transient neonatal HI (TNHI) is well described in small for gestational age (SGA) and asphyxiated newborns [5, 6, 7, 10, 11,19]. Additionally, HI occurs and resolves within 1 or 2 days in neonates born to mothers with poorly controlled diabetes [13,22]. Infants with Beckwith-Wiedemann syndrome (BWS) have β-cell hyperplasia and may experience either prolonged or transient HI [16]. Other very rare causes of TNHI are Rhesus or platelet isoimmunisation [1,4], sepsis, cerebral haemorrhage, severe stress and the hyperinsulinism-hyperammonaemia (HI/HA) syndrome [23]. To our knowledge, TNHI has not been reported so far in neonates without perinatal complications and with normal birth size parameters.

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We report transient HI, presenting as a severe phenotype of congenital HI, in two neonates born appropriate for gestational age (AGA) with largely uneventful antenatal and birth histories.

Case reports

Case 1

This girl was born at 34 weeks gestation to non-consanguineous Caucasian parents with a birth weight of 2,275 g (50th–75th percentile). An uncomplicated caesarean section was performed because of reduced fetal movements. Apgar scores were 9 at both 1 and 5 min. The pregnancy was uneventful except for mild pregnancy-induced hypertension, which did not require anti-hypertensive therapy. Four hours after birth, she developed respiratory distress and a blood glucose level (BGL) taken was 0 mmol/l, which was transiently stabilised with glucose and glucagon infusions. A critical sample taken at a BGL of 1.5 mmol/l demonstrated normal growth hormone and cortisol responses of 173 mIU/l and 414 nmol/l, respectively. There was insufficient blood for insulin levels. Persistent hypoglycaemia required glucose infusions up to 24 mg/kg per min and glucagon infusions up to 35 μg/kg per h. Intravenous hydrocortisone, up to 10 mg/kg per day, was administered to provide an insulin resistant effect. An intravenous infusion of Octreotide was commenced at 0.5 μg/kg per h and titrated upwards to a dose of 4 μg/kg per h. This was ceased after 24 h because of concerns about abdominal distension and the potential risk of necrotising enterocolitis in view of her borderline gestation. Proper umbilical venous catheter (UVC) positioning avoided direct stimulation of insulin secretion by local glucose flooding. However, even after the UVC was replaced by a femoral venous line, no improvement was evident. On day 2 of life, plasma insulin was >200 mU/l at a BGL of 2.0 mmol/l, indicating an inappropriate and markedly elevated serum insulin level. Subsequent paired insulin/glucose samples on day 3 were >200 mU/l/1.9 mmol/l and 146 mU/l/2.6 mmol/l. The serum ammonia level was normal. Amino acid and organic acid screening excluded underlying metabolic disorders. Oral diazoxide was commenced on day 5 at a dose of 10 mg/kg per day when abdominal signs abated. Progressive reduction in dextrose and glucagon requirements ensued from day 6 onwards. Glucagon, diazoxide and hydrocortisone were ceased on days 10, 12 and 13 of life respectively, without recurrence of hypoglycaemia. On day 15, a 6-h fast was well tolerated without hypoglycaemia and no subsequent hypoglycaemic episodes were observed (Fig. 1). BGL on follow-up have been consistently above 3.5 mmol/l.

Case 2

This girl was born at 38 weeks to a non-consanguineous Caucasian couple after an uneventful pregnancy by normal vaginal delivery. She had a length of 48 cm (25th–50th percentile), a weight of 3,070 g (25th–50th percentile) and Apgar scores of 9 and 10 at 1 and 5 min. Signs and symptoms of hypoglycaemia (sweating, jitteriness, irritability, poor feeding and vomiting) were observed within the first 2 days of life, before transfer to our hospital. The BGL was 2.0 mmol/l at 1 h of life and varied from 2.6 mmol/l at 4 h after birth to 0.66 mmol/l at 48 h. There were no signs of asphyxia or neonatal infections with normal full blood count and blood gas analysis. Despite oral feeds and several boluses of glucose, BGL levels could not be kept within the normal range. After transfer, a continuous glucose infusion of up to 22.1 mg/kg per min was necessary to obtain normoglycaemia. A critical sample obtained on the 3rd day of life revealed markedly elevated serum insulin levels (40 mU/l) in the presence of hypoglycaemia (0.8 mmol/l) and appropriately elevated levels of growth hormone and cortisol. Ammonia levels were normal. Amino acid and organic acid screening excluded underlying metabolic disorders. A 3-day course of dexamethasone (0.23 mg/kg per day) and the introduction of diazoxide (9.3 mg/kg per day) on day 10 led to a gradual reduction of intravenous glucose requirement. The infusion could be stopped on day 15. Diazoxide was tapered down and stopped at day 90 without clinical or biochemical evidence of hypoglycaemia. At age 4 months, her BGL was 3.2 mmol/l after a 9.5 h fast with subsequent fasting BGLs averaging 3.9 mmol/l. She has remained well since (Fig. 1).

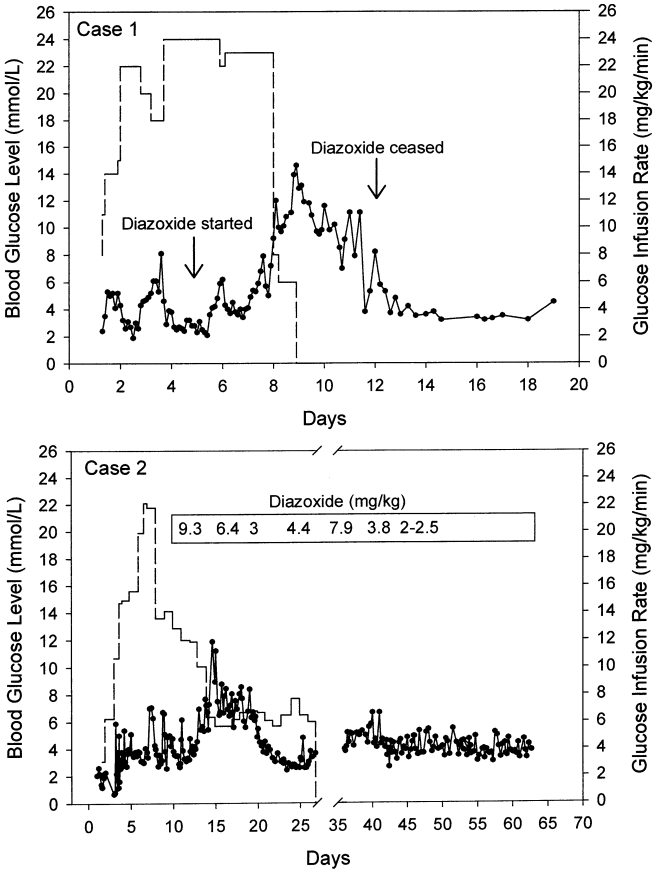

Fig. 1 Time course of BGL (*black dots*) and glucose infusion rates (*dashed lines*) after birth for cases 1 and 2

Discussion

We describe two cases of TNHI without predisposing factors such as intrauterine growth retardation (IUGR), maternal diabetes and perinatal asphyxia or other rare associated conditions. The unusual diazoxide sensitivity in these babies with neonatal-onset HI narrows the differential diagnosis to idiopathic TNHI or HI due to glutamate dehydrogenase overactivity [23] and facilitates differentiation of transient from persistent forms of HI. Our cases suggest that there is a wider spectrum of conditions causing TNHI, the aetiology of which is often unknown and may represent mild forms of PHHI.

To date, TNHI has been exclusively reported in neonates born to mothers with poorly controlled type 1 or gestational diabetes [22], in neonates with IUGR/SGA [7], in severe perinatal stress secondary to asphyxia

neonatorum [5, 6, 10, 11,19] or rhesus/platelet isoimmunisation [1,4]. The pathogenetic mechanism for HI in infants of diabetic mothers is best understood. In this instance, sustained fetal hyperglycaemia leads to insulin hypersecretion, which persists after birth leading to neonatal hypoglycaemia that resolves after several days [17,20]. HI in SGA or asphyxiated infants is usually more prolonged and can persist for several months [6]. It has been suggested that a combination of asphyxia and SGA predispose to more severe and prolonged HI and hypoglycaemia [3]. Although the aetiology of HI in this group of infants remains an enigma, it is clear that their hypoglycaemia is part of a multifactorial phenomenon, which includes glycogen depletion, impaired gluconeogenesis and increased glucose demand and utilisation [3].

Our cases illustrate that transient HI can occur in neonates born without a history of gestational diabetes or perinatal asphyxia and with a birth weight that is AGA. The absence of increased birth weight indicates that HI was not prolonged during intrauterine life and makes BWS unlikely. The serum ammonia levels were not elevated, excluding regulatory abnormalities of the glutamate dehydrogenase gene [23]. Such ''idiopathic'' forms are not well described in the literature and are likely to represent abnormal β-cell function [18]. An underlying genetic basis is possible, as a heterozygous mutation has been described in a neonate with transient HI [8].

Limited information can be extrapolated from the largest reported data series on neonatal-onset HI [8], while other series exclude TNHI from their analysis [15]. In the former series, the probability of resolution of HI was about one in eight babies. In the 12 neonates with TNHI listed, 9 did not require diazoxide, while the other three were sensitive to the drug, with complete resolution of HI within 1 month. These cases seem to suggest that the phenotype of TNHI is more mild than severe.

Both cases we describe developed severe symptomatic hypoglycaemia within the first hours of life, which persisted and required aggressive medical treatment for 7 to 15 days. Glucose and glucagon infusion requirements were very high, reflecting the markedly elevated plasma insulin levels in both cases, and suggesting the possibility of a severe persistent phenotype of PHHI. The unusual feature was the dramatic response to diazoxide therapy, given that diazoxide unresponsiveness is associated with higher levels of insulin [24], as seen in our neonates. The combination of neonatal-onset hypoglycaemia, diazoxide sensitivity and transient HI is rare but not unique to our babies [24], although many reported cases involve acquired HI secondary to IUGR/SGA [3] or asphyxia neonatorum [5,26].

Diazoxide is an essential drug in the treatment of hyperinsulinaemic hypoglycaemia [2,9]. Additionally, sensitivity to diazoxide is an important indicator in the diagnostic process of neonatal-onset HI because, in contrast to PHHI, transient cases usually respond well to diazoxide and do not require surgery [21]. Furthermore, diazoxide sensitivity confirms the functional integrity of the β-cell sulphonylurea receptor type 1 (*SUR1*) as well as the inward-rectifying potassium channel (*KIR6.2*) genes, as the majority of patients with *SUR1* and *KIR6.2* mutations are resistant to diazoxide [8].

The existence of severe forms of TNHI reinforces the importance of maintaining medical treatment of hypoglycaemia for a sufficient duration, even in the most severely affected patient, particularly in diazoxide-sensitive neonates. Therefore, allowing a period of at least 4 weeks to elapse before contemplating pancreatic surgery is important in order to exclude TNHI [14]. Pancreatic venous sampling should be carried out prior to surgery to distinguish between focal and diffuse disease [2,8], as sporadic hyperinsulinaemic hypoglycaemia is histologically heterogenous [8].

In conclusion, diazoxide-sensitive neonatal-onset hyperinsulinaemic hypoglycaemia is uncommon but suggestive of transient HI. TNHI occurring in neonates delivered uneventfully without a history of predisposing factors are mild in most instances, but can mimic the classical PHHI phenotype when severe. Careful consideration of the indication, timing and extent of pancreatectomy is required, taking into account current management guidelines [2, 8,14], while maintaining euglycaemia to protect the developing brain.

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