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Unusual association of diseases/symptoms

Neonatal hyperinsulinism secondary to maternal intake of high-sugar drinks

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Summary

The authors report a macrosomic term male infant who developed refractory hyperinsulinism requiring 20 mg/kg/min intravenous dextrose (usual range 4–6 mg/kg/min) and treatment with diazoxide 10 mg/kg/day. His blood insulin level at 6 h of age was 22.3 mU/l (reference range <5 mU/l) with corresponding laboratory blood glucose of 0.3 mmol/l. There was no detected maternal diabetes but the mother revealed she drank 2 l of 'lucozade energy' a day in the past 3 months of pregnancy. The hyperinsulinism resolved by day 7. Transient neonatal hyperinsulinism is known to be associated with maternal diabetes but has not previously been reported as secondary to high maternal sugar intake. This case highlights that significant hypoglycaemia secondary to transient hyperinsulinism can occur in infants of mothers without identified diabetes.

BACKGROUND

This is a report of a neonate who developed significant hypoglycaemia and hyperinsulinism after birth. During her late pregnancy the mother had been drinking large amounts of a high sugar drink. She was not identified as having diabetes in pregnancy. There is no specific national guidance that a high sugar intake in pregnancy is potentially harmful to the fetus. We felt this report was important to highlight this issue. It also demonstrates that infants can present with hypoglycaemia secondary to a transient hyperinsulinism even if there is no history of maternal diabetes, which can have a significant morbidity and mortality.

CASE PRESENTATION

We report a macrosomic term male infant who developed refractory hyperinsulinism requiring 20 mg/kg/min intravenous dextrose (usual range 4–6 mg/kg/min) and treatment with diazoxide 5 mg/kg/day. His blood insulin level at 6 h of age was 22.3 mU/l (reference range <5 mU/l) with corresponding laboratory blood glucose of 0.3 mmol/l. Echocardiography demonstrated ventricular septal hypertrophy. There was no maternal history of diabetes but the mother revealed she drank 2 l of 'lucozade energy' a day in the last 3 months of pregnancy which contains 174 g glucose in 2 l. WHO recommended daily amount is around 50 g (10% of diet).

The hyperinsulinism resolved by day 7. Investigation did not reveal an alternative cause. Transient neonatal hyperinsulinism is known to be associated with maternal diabetes but has not previously been reported to be caused by high maternal sugar intake without the detection of diabetes.

The patient was the first child of his 23-year-old mother. She had no medical concerns during her pregnancy. She had normal booking bloods and normal 20 week ultrasound scan. She required no further antenatal scans. She did not have evidence of gestational diabetes on urine dipstick, although blood tests such as glycosylated haemoglobin level were not checked before or after delivery. She was on no medication and was not identified as having a high BMI. She developed hypertension and proteinuria 3 days before delivery. There was rupture of membranes 72 h before delivery and she had a raised C reactive protein (CRP). Labour was augmented 12 h before vaginal delivery at term.

Birth weight was 3.910 kg on 75th–91st centile with a head circumference of 36.5 cm on 75th–91st centile. He required no resuscitation at birth with apgars of 8 at 1 min and 10 at 5 min. Blood glucose remained <2.4 mmol/l up to 6 h of age despite breast and bottle feeds.

He was noted at this point to be jittery and blood glucose was identified as 1.8 mmol/l. He was given an intravenous bolus 10% dextrose followed by 10% dextrose 60 ml/kg/day. A full sepsis screen was taken which revealed a CRP of 3 mg/l and cerebrospinal fluid and blood cultures were later negative. A chest x-ray was normal. He had no evidence of haemolysis. His CRP rose later to 38. Glucose levels remained suboptimal and over 24 h intravenous dextrose was increased to 90 ml/kg/day 15% dextrose and then to 20% dextrose at 120 ml/kg/day via a central umbilical line. This is a rate of 20 mg/kg/min (usual requirement 4–6mg/kg/min). With this blood glucose levels were consistently normal. However, hyponatraemia developed secondary to fluid overload. On clinical examination, he was oedematous and had a systolic murmur. Echocardiography revealed a patent ductus arteriosus as well as intraventricular septal hypertrophy.

On day 2, the hypoglycaemia screen had revealed a raised insulin level. On discussion with tertiary paediatric endocrinology team diazoxide was commenced at 5 mg/kg twice daily. This was started in part due to the problems of fluid overload on the high volume of intravenous 20% dextrose and also because of identified hyperinsulinism. From day 2 blood glucose levels remained normal and the dextrose and diazoxide requirements were gradually

reduced until ceasing on day 7. By then he had established full enteral feeds.

During the first day the mother revealed that she drank 2 l of lucozade a day for past 3 months of pregnancy. Two litres of 'lucozade energy' contains 176 g glucose. WHO recommend daily sugar intake of 48 g (10% of diet).

INVESTIGATIONS

Insulin level 22.3 (normal <5), C-peptide 2751 (normal <600). Organic and amino acids, acyl carnitine, 17 OH progesterone, ammonia and lactate were normal. Growth hormone appropriately raised at >96, no urinary ketones. Repeat ECHO revealed closing patent ductus arteriosus and bulky intraventricular tissue.

DIFFERENTIAL DIAGNOSIS

Neonatal hypoglycaemia as defined as a serum glucose level of 2.6 mmol/l or lower is a common occurrence, particularly in the few hours post delivery. It is considered pathological if it is persistent despite feeding or associated with clinical symptoms of hypoglycaemia. It is important to identify and manage hypoglycaemia promptly as clinical effects can be severe. These include seizures, coma and death. Neonatal hypoglycaemia has been found to be associated with adverse long-term neurological effects, as have neonatal seizures independently.[1 2]

Neonatal hypoglycaemia can be caused by several different mechanisms. It is a frequent complication in small or preterm infants and is secondary to reduced glycogen stores. Blood glucose levels should also be monitored in sick infants because they have increased glucose requirements. It can be secondary to a reduced ability to transport glucose to the required cells, this occurs in hypoxic brain injury which affects glucose transporters. It can also occur in many metabolic disorders such as galactosaemia, organic acidaemias, glycogen storage disorders and fatty acid oxidation defects. Hypoglycaemia also commonly occurs in an infant because of inadequate intake – such as a period of reduced feeding.

Hyperinsulinism is an important cause of neonatal hypoglycaemia and as demonstrated by this case can cause a severe, refractory hypoglycaemia. Hyperinsulinism can be transient or prolonged. Causes of prolonged hyperinsulinism include focal and diffuse pancreatic adenomatous hyperplasia and are associated with several gene defects which result in increased Ø-2 cell insulin production. The more common mutation, SUR K channel produces a severe, diazoxide resistant hyperinsulinism. The second most common mutation causes the hyperinsulinism/hyperammonaemia syndrome which may have a milder clinical course.[3]

There are many causes of transient neonatal hyperinsulinism. The most common is secondary to a mother with diabetes. This is because glucose freely passes into the placenta from the maternal circulation, and the neonatal pancreas responds by increasing insulin secretion and becoming hypertrophied. On delivery, the maternal glucose supply stops and it takes time for the neonatal pancreas to adjust. It can cause significant hypoglycaemia, but normally resolves in a period of days.

Other causes include intrauterine growth retardation, perinatal asphyxia and rhesus isoimmunisation. The hyperinsulinism secondary to these causes appears to often take longer to resolve. Beckwith–Wiedemann syndrome also causes a transiently increased insulin secretion secondary to increased insulin-like growth factor 2 expression. The infant in this report did not have the clinical features of this condition. Umbilical artery catheterisation has also been linked, thought to be secondary to increased glucose load to the coeliac axis. In this case, the high insulin level was detected before catheter insertion. The baby in this case report did have a raised CRP suggesting an infection, although cultures were negative. Sepsis is linked with reduced insulin sensitivity and hyperglycaemia so is unlikely to explain the hyperinsulinism.

One study found an association with high neonatal serum lactate levels.[4] The cases resolved within a period of 3 – 4 weeks. This baby's lactate level was not elevated – 2.6 mmol/l at birth. Eight of 54 babies with parents who had diabetes caused by HNF4A mutation had transient hypoglycaemia - 3 with hyperinsulinism and were found to be heterozygous for the mutation. In this patient, neither parent had a history of diabetes.[5] There is a published report of two cases of transient neonatal hyperinsulinism with no identified gestational or other recognised cause.[6] They did not report on maternal diet. Both responded quickly to diazoxide.

Hyperinsulinism/hyperammonaemia syndrome was also considered. The initial ammonia level was 108, repeat at 6 months age was normal. On assessment at 6 months of age he was a well, thriving baby with normal fasting glucose level.

TREATMENT

The infant with hypoglycaemia may present with jitteriness, poor feeding, irritability, respiratory distress, apnoea, hypothermia, seizures and coma. Initial management depends on if the baby is symptomatic and degree of hypoglycaemia. As it is common to identify blood glucose levels under 2.6 mmol/l soon after birth current UK guidelines advise that for infants of diabetic mothers to check levels 2–4 h after birth, but recommend early feeding.[7] If the blood glucose level is low then management is often initially with feeding, including naso/oro-gastric tube feeds if required. Particularly if there is no history of maternal diabetes, consideration is given to performing a screen for sepsis and commencing antibiotics. This is because hypoglycaemia can be secondary to illness. Another consideration is to performing a screen for metabolic causes of hypoglycaemia – which would include an insulin level.

If feeds are unsuccessful or not tolerated or if the baby has symptoms of hypoglycaemia intravenous dextrose is instituted, initially with 10% dextrose. Concentration and volume may need to be increased. If concentrations over 12.5% dextrose are used a central line is recommended. Consultation with a paediatric endocrinology team is useful. In cases of identified hyperinsulinism, diazoxide is often effective as it directly inhibits insulin release. Glucocorticoids are generally no longer used as they have not been shown to always be effective.[8] Glucagon infusions can be used for a period of a few days. Ultimately, in severe, persistent hypoglycaemia secondary to hyperinsulinism, which is usually secondary to a genetic cause or focal pancreatic adenoma, pancreatectomy or partial pancreatectomy may be required.

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OUTCOME AND FOLLOW-UP

Follow-up at 6 months of age revealed a thriving baby with a normal fasting glucose and normal ammonia level. One year cardiac follow-up revealed resolving intraventricular septal hypertrophy.

DISCUSSION

What is known about neonatal hyperinsulinism and maternal glucose tolerance?

There is established evidence of neonatal hyperinsulinism secondary to maternal diabetes but no published reports of hyperinsulinism secondary to isolated high maternal sugar intake. It is possible that she could have had a degree of insulin resistance but still with normal urinalysis as found on routine antenatal care.

Westgate detected raised cord insulin levels of 5.6 –13.0 mU/l (40 – 94 pmol/l) in mothers with gestational diabetes, even with normal glucose tolerance postpartum.[9] Jensen found no significant trend between maternal glucose intolerance (2 h glucose <9) and neonatal hypoglycaemia, but did with macrosomia and preterm delivery.[10]

Schafer-Graf found higher cord blood insulin levels in mothers with impaired glucose tolerance then controls.[11] However, Pirc found no difference in cord blood insulin levels between mothers with mild gestational diabetes and controls after diet advice.[12]

The HAPO group studied glucose levels in non-diabetic mothers at 28 weeks gestation and found a strong association with maternal fasting glucose values and foetal size and hyperinsulinism at birth, and a significant association of neonatal hypoglycaemia with the 1 h maternal oral glucose tolerance test level.[13]

Neonatal ventricular septal hypertrophy is a known potential consequence of maternal diabetes. Demiroren *et al* also demonstrate its presence in macrosomic babies with no history of maternal diabetes.[14] Way *et al* showed this abnormality tends to normalise by the end of the first year of life.[15]

CONCLUSIONS

This is a report of significant neonatal hypoglycaemia secondary to hyperinsulinism. It may be related to maternal high glucose intake in pregnancy. The mother was not identified as having developed diabetes in pregnancy. The baby had a significant risk of morbidity and mortality.

There is current evidence that reduced maternal glucose tolerance, even at levels not considered to be clinically significant is associated with raised neonatal insulin levels. This report demonstrates the extent of neonatal hypoglycaemia that may occur.

In the UK, there is clear advice given for alcohol and caffeine intake in pregnancy. UK NICE guidelines 2008 state the 'importance of a balanced diet' but do not specify sugar intake.[16] Routine screening for diabetes is recommended if there is a high BMI, previous macrosomic baby, previous gestational diabetes, family history of diabetes or family origin with a high prevalence of diabetes. This mother did not qualify for screening. It is possible that she could have developed a degree of insulin resistance not detected on urinalysis. The purpose of this article is not so much to describe a new mechanism for neonatal hyperinsulinism but more to demonstrate that significant hyperinsulinism may occur in infants of mothers not identified as having established diabetes.

The mother was unaware of the amount of sugar she was ingesting or that her high sugar diet might be harmful. We propose that consideration could be made to including in routine antenatal advice that a high dietary sugar intake in late pregnancy could have the risk of causing harm to the baby, even in mothers not screened for or identified as having diabetes.

Learning points

- Neonatal hyperinsulinism can cause profound and refractory hypoglycaemia with the potential for serious harm to the baby.
- In the symptomatic hypoglycaemic neonate it is important to establish normal blood sugar levels promptly to avoid short and long-term neurological complications.
- Neonatal hyperinsulinism is most commonly a transient phenomenon secondary to maternal diabetes. However, both transient and prolonged neonatal hyperinsulinaemic hypoglycaemia may occur secondary to a variety of pathologies, including in infants with no identifiable risk factors.
- It is well established that neonatal hyperinsulinism is associated with maternal diabetes but has not previously been linked with isolated high maternal sugar intake in pregnancy.

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Competing interests None.

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REFERENCES

1. **Stenninger E,** Flink R, Eriksson B, *et al*. Long-term neurological dysfunction and neonatal hypoglycaemia after diabetic pregnancy. *Arch Dis Child Fetal Neonatal Ed* 1998;**79**:F174–9.
2. **McBride MC,** Laroia N, Guillet R. Electrographic seizures in neonates correlate with poor neurodevelopmental outcome. *Neurology* 2000;**55**:506–13.
3. **Palladino AA,** Bennett MJ, Stanley CA, *et al*. Hyperinsulinism in infancy and childhood: when an insulin level is not always enough. *Clin Chem* 2008;**54**:256–63.
4. **Hussain K,** Thornton PS, Otonkoski T, *et al*. Severe transient neonatal hyperinsulinism associated with hyperlactataemia in non-asphyxiated infants. *J Pediatr Endocrinol Metab* 2004;**17**:203–9.
5. **Pearson ER,** Boj SF, Steele AM, *et al*. Macrosomia and hyperinsulinaemic hypoglycaemia in patients with heterozygous mutations in the HNF4A gene. *PLoS Med* 2007;**4**:e118.
6. **Yap F,** Högler W, Vora A, *et al*. Severe transient hyperinsulinaemic hypoglycaemia: two neonates without predisposing factors and a review of the literature. *Eur J Pediatr* 2004;**163**:38–41.
7. NICE. Diabetes in Pregnancy Prevention and Assessment of Neonatal Hypoglycaemia. London: NICE, 2008. http://guidance.nice.org.uk/CG63 (Accessed 30 March 2010)
8. **Sperling M**. *Pediatric Endocrinology*. Philadelphia, PA: Saunders Elsevier Publications 2008.
9. **Westgate JA,** Lindsay RS, Beattie J, *et al*. Hyperinsulinemia in cord blood in mothers with type 2 diabetes and gestational diabetes mellitus in New Zealand. *Diabetes Care* 2006;**29**:1345–50.
10. **Jensen DM,** Korsholm L, Ovesen P, *et al*. Adverse pregnancy outcome in women with mild glucose intolerance: is there a clinically meaningful threshold value for glucose? *Acta Obstet Gynecol Scand* 2008;**87**:59–62.

11. **Schäfer-Graf UM,** Dupak J, Vogel M, *et al*. Hyperinsulinism, neonatal obesity and placental immaturity in infants born to women with one abnormal glucose tolerance test value. *J Perinat Med* 1998;**26**:27–36.
12. **Pirc LK,** Owens JA, Crowther CA, *et al*. Mild gestational diabetes in pregnancy and the adipoinsular axis in babies born to mothers in the ACHOIS randomised controlled trial. *BMC Pediatr* 2007;**7**:18.
13. Hapo Study Cooperative Research Group. The hyperglycaemia and adverse pregnancy outcome (HAPO) study. *Int J Gynecol Obstet* 2002;**78**:69–77.
14. **Demiroren K,** Cam L, Oran B, *et al*. Echocardiographic measurements in infants of diabetic mothers and macrosomic infants of nondiabetic mothers. *J Perinat Med* 2005;**33**:232–5.
15. **Way GL,** Wolfe RR, Eshaghpour E, *et al*. The natural history of hypertrophic cardiomyopathy in infants of diabetic mothers. *J Pediatr* 1979;**95**:1020–5.
16. NICE. Antenatal Care: Routine Care for the Healthy Pregnant Woman. London: NICE 2008. http://guidance.nice.org.uk/CG62 (Accessed 21 June 2010)