PedsCases Podcast Scripts

This is a text version of a podcast from Pedscases.com on "**Neonatal Hypoglycaemia – CPS Podcast.**" These podcasts are designed to give medical students an overview of key topics in pediatrics. The audio versions are accessible on iTunes or at www.pedcases.com/podcasts.

Neonatal Hypoglycaemia – CPS Podcast

Developed by Carina Lauzon, Dr. Michael Narvey, and Dr. Marc-Antoine Landry for PedsCases.com.
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Introduction

Hi everyone, my name is Carina Lauzon and I am a fourth-year medical student at the University of Alberta. This PedsCases Canadian Pediatric Society podcast is designed to give an organized approach to neonatal hypoglycaemia, the most common metabolic problem in neonates and the leading cause of admissions to the neonatal intensive care unit. This podcast is based on the 2019 Canadian Pediatric Society statement, *The screening and management of newborns at risk for low blood glucose.*

This podcast was created with Dr. Michael Narvey, who is section head of neonatology at the University of Manitoba and co-author of the CPS statement, and Dr. Marc-Antoine Landry, a neonatologist at the Royal Alexandra Hospital in Edmonton, Alberta.

Clinical Case

Let's start with a clinical case: you are on your NICU rotation and you are called to see baby Rachel, who was born two hours ago, at 39 weeks gestation, to a mother with gestational diabetes. Apart from gestational diabetes, Rachel's mother's pregnancy and Rachel's birth were uneventful. You are called because Rachel has a blood glucose level of 2.2 mmol/L at 2 hours of age. Considering what you know about this patient, what should your next steps be? We will review the answer to this case at the end of the podcast.

Objectives

After listening to this podcast, the learner will be able to:

1. Recognize which infants are at risk for neonatal hypoglycaemia
2. Know how to diagnose transitional and persistent neonatal hypoglycaemia
3. Know the signs and symptoms of neonatal hypoglycaemia
4. Recognize which infants should be screened for neonatal hypoglycaemia and know how screening should be performed
5. Know how to manage transitional and persistent neonatal hypoglycaemia

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Normal Glucose Homeostasis

We will start with an overview of normal glucose homeostasis. Maintaining appropriate blood glucose levels is extremely important. The brain uses glucose as its primary fuel to meet its metabolic needs and therefore, sustained hypoglycaemia or very low glucose levels can lead to brain damage.

The main hormones responsible for control of blood glucose are insulin and glucagon, but epinephrine, cortisol, and growth hormone also play a role in glucose homeostasis. In response to high blood glucose levels, insulin secretion from beta cells in the pancreas is increased and this stimulates the liver to store glucose as glycogen. When blood glucose levels are low, glucagon secretion from pancreatic alpha cells is increased and this stimulates glycogenolysis and gluconeogenesis, therefore increasing the release of glucose into the bloodstream. During times of starvation, amino acids from muscle stores can be used for gluconeogenesis and fatty acids can be broken down to produce ketone bodies, an alternate fuel source for the tissues of the body, including the brain. Starvation also stimulates the sympathetic nervous system, thus causing the release of epinephrine from the adrenal glands, which increases the release of glucose from the liver. Finally, in periods of prolonged hypoglycaemia, the body secretes growth hormone and cortisol; these hormones reduce the rate at which the body utilizes its limited glucose supply.

In utero, the fetus receives a constant supply of glucose from its mother via facilitated diffusion through the placenta. The fetus produces its own insulin in order to maintain glucose homeostasis in the womb. After birth, the constant supply of glucose that the baby was receiving from its mother stops abruptly, and therefore, in order to prevent hypoglycaemia, neonatal secretion of insulin must be regulated.

In the healthy newborn, serum glucose levels will drop in the first 2-3 hours of life, then will spontaneously increase and subsequently be maintained by regular feedings. It is not unusual to see low blood glucose levels in the first 24-48 hours of life, as the baby adjusts to life outside the womb. This is called transitional hypoglycaemia and is seen in up to 10% of healthy term infants. In asymptomatic babies without risk factors for neonatal hypoglycaemia, which we will discuss later in the podcast, these brief periods of low blood glucose are assumed to be benign.

Defining Neonatal Hypoglycemia

Transition-related hypoglycaemia is defined as blood glucose levels below 2.6 mmol/L in the first 72 hours of life, and persistent hypoglycaemia is defined as blood glucose levels below 3.3 mmol/L after 72 hours of age. However, it is difficult to determine exactly what blood glucose level indicates neonatal hypoglycaemia, as a single number cannot be applicable to all infants and all situations. The blood glucose at which hypoglycaemia occurs depends on the infant's size, gestation, clinical condition, availability of energy sources and energy demand.

The clinical presentation of neonatal hypoglycaemia can range from a completely asymptomatic infant to severe central nervous system and cardiopulmonary

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disturbances. There are two general categories of symptoms of neonatal hypoglycaemia: neurogenic and neuroglycopenic.

The neurogenic symptoms happen as a result of sympathetic nervous system stimulation in response to hypoglycaemia, so are also called adrenergic signs. They are the first symptoms to appear, occurring at higher blood glucose concentrations than the neuroglycopenic symptoms. The neurogenic symptoms include jitteriness, pallor, temperature instability, irritability, and tachycardia.

The neuroglycopenic symptoms happen as a result of decreased glucose delivery to the brain and include episodes of cyanosis, convulsions, intermittent apneic spells or tachypnea, a weak or high-pitched cry, hypotonia, lethargy, and coma that may lead to death if the hypoglycaemia is not corrected.

Severe, recurrent neonatal hypoglycaemia can cause permanent brain damage, which can lead to cognitive abnormalities, cerebral palsy, personality disorders, and occipital lobe epilepsy.

Because other conditions such as sepsis can cause similar symptoms to hypoglycaemia, it is important to document hypoglycaemia and confirm whether symptoms resolve with administration of glucose.

Risk factors/Causes for Neonatal Hypoglycaemia

The most important risk factors for neonatal hypoglycaemia can be grouped into three categories: babies who are too large, too small, or too sick. Infants that fall in the “too large” category include infants who are large for gestational age (LGA, >90th percentile) and infants of diabetic mothers. Infants who fit in the “too small” category include infants who are small for gestational age (SGA, <10th percentile), those who suffer from intrauterine growth restriction (IUGR), and those who are born prematurely (<37 weeks). Infants who suffer from sepsis and infants of mothers with eclampsia or chorioamnionitis are also at an increased risk for hypoglycaemia. Maternal labetolol use, asphyxia and late preterm exposure to antenatal steroids are additional risk factors.

The two most common causes of neonatal hypoglycaemia are excess insulin production and inadequate glycogen stores: in both of these situations, gluconeogenesis is impaired.

Excess insulin production, or hyperinsulinism, is the most common cause of neonatal hypoglycaemia. Hyperinsulinism frequently occurs in infants in the “too large” category, including infants of diabetic mothers and macrosomic infants (infants who weigh over 4kg at birth). These infants receive a large supply of glucose from their mothers in utero and therefore must produce a large amount of insulin in order to maintain glucose homeostasis. This can cause hypoglycaemia after birth, as the infant continues to produce large amounts of insulin in the absence of the large glucose supply. A rarer cause of hyperinsulinism is a congenital disorder called Persistent Hyperinsulinism Hypoglycaemia of Infancy (PHHI), in which the normal relationship between blood glucose levels and insulin secretion is disturbed and insulin is released even at low blood glucose levels. Other less common conditions such as Beckwith-Wiedemann syndrome and Sotos syndrome can also lead to hyperinsulinism.

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Inadequate glycogen stores are another common cause of neonatal hypoglycaemia. Infants who are in the “too small” category, such as those born prematurely (<37 weeks), those who are small for gestational age (SGA) or those with intrauterine growth restriction may have low hepatic glycogen stores, low muscle stores, and low lipid stores to be used as substrates for gluconeogenesis and ketogenesis. Similarly, infants who experience perinatal asphyxia or starvation may deplete their glycogen stores and therefore be unable to produce glucose through gluconeogenesis.

Other less common causes of neonatal hypoglycaemia include increased glucose use (which can happen as a result of hypothermia, sepsis or polycythemia), growth hormone deficiency, cortisol deficiency, inborn errors of metabolism, adrenal insufficiency, liver disease, poisonings or drugs, and systemic disease.

Screening

Because neonatal hypoglycaemia can lead to severe consequences, it is important to know which babies should be screened. For the purposes of screening, the Canadian Pediatric Society recommends using a cut-off of 2.6 mmol/L for at risk infants in the first 72 hours of life, as blood glucose levels below this are associated with adverse outcomes, especially if persistent or repeated.

During the first two hours of life, infants should not be screened for neonatal hypoglycaemia unless they are unwell or symptomatic. If they are unwell or symptomatic and have a blood glucose level of below 2.6 mmol/L, the infant should not be fed and treatment should be initiated immediately.

After two hours of age, if the infant is well and is not at risk for neonatal hypoglycaemia, routine care should be given, including feeding on demand. The infant should not be tested unless they become unwell.

In infants who are at risk for neonatal hypoglycaemia (LGA, infant of a diabetic mother, SGA, IUGR, or preterm), blood glucose levels should be checked at two hours of age, after at least one effective feed, and then every 3-6 hours after that, before feeds, provided that the infant remains well and glucose levels are stable. In at risk infants, we aim for blood glucose levels above 2.6 mmol/L in the first 72 hours of life. If the infant’s glucose level is <2.6 mmol/L, treatment should be considered. When blood glucose levels are greater than 2.6 mmol/L, the child should be fed on demand. In this case, treatment is not indicated, however, glucose levels should continue to be monitored prior to feeds.

In infants of diabetic mothers or those who are large for gestational age, hypoglycaemia usually happens within the first 12 hours of life. Therefore, glucose testing can be stopped if levels have been consistently above 2.6 mmol/L at 12 hours of age. In infants who are small for gestational age or premature, hypoglycaemia usually happens within the first 24 hours of life. In these cases, testing can be discontinued if glucose levels are consistently above 2.6 mmol/L and regular feeds have been established by 24 hours of age.

Management

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In the next section of this podcast, the management of neonatal hypoglycaemia, I am joined by Dr. Michael Narvey, section head of neonatology at the University of Manitoba and co-author of the CPS Statement, *The screening and management of newborns at risk for low blood glucose.*

Q: Dr. Narvey, what are some treatment options for neonatal hypoglycaemia?
Treatment methods for neonatal hypoglycaemia include increased breastfeeding frequency, supplementation with donor breast milk, formula, or 40% dextrose gel, IV glucose, and, in persistent cases, pharmacological intervention. Frequent breastfeeding on demand should be encouraged in at risk infants in an attempt to prevent neonatal hypoglycaemia. If mild hypoglycaemia occurs, increased frequency of feeding plus or minus supplementation may be all that is needed to help the infant return to a euglycaemic state.

Q: If an infant screens positive for neonatal hypoglycaemia but is asymptomatic, how should they be treated?

If an infant is asymptomatic and has a glucose level <2.6mmol/L at 2 hours of age, the infant may receive 0.5mL/kg of 40% dextrose gel with a feed. Alternatively, for those centres not employing dextrose gels a breastfeed and measured volume of 5 mL/kg of a feed may be offered. Glucose levels should be re-checked 30 minutes after the feed. After this, if glucose levels are below 1.8mmol/L or the infant is not tolerating feeds, IV dextrose therapy should be considered. If glucose levels are between 1.8mmol/L and 2.6 mmol/L, the infant should receive another dose of 40% dextrose gel and another feeding or breastfeed with an increased measured volume of 8 mL/kg.. If blood glucose levels are still <2.6mmol/L 30 minutes after this feed, IV therapy should be considered.

Q: What if an infant is symptomatic?
If an infant is unwell or symptomatic and has a blood glucose level of below 2.6 mmol/L, the infant should not be fed and treatment with IV dextrose should be initiated immediately. In symptomatic infants, 40% dextrose gel may be used as a temporizing measure to raise blood glucose while waiting to establish an IV.

Q: How do you manage a baby who requires IV dextrose therapy?

When initiating IV therapy, The Canadian Pediatric Society recommends starting with a 10% dextrose solution at 80 mL/kg/day, which is equivalent to 5.5mg/kg/min of glucose. A single bolus of 2mL/kg 10% dextrose solution over 15 minutes can be used to reach target glucose levels more quickly, particularly when a baby is symptomatic. Blood glucose should be checked 30 minutes after initiation of IV therapy. If blood glucose is greater than 2.6mmol/L, it should continue to be monitored every 3 hours. When glucose levels are above 2.6 mmol/L, enteral feeds can be introduced as tolerated, and IV dextrose therapy may be slowly weaned when levels have been stable for 12 hours. Pre-feed glucose monitoring should continue until the infant is on full enteral feeds and 2 consecutive blood glucose levels have been >3.3mmol/L.

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If blood glucose levels are <2.6mmol/L after 30 minutes of IV therapy, the rate of infusion can be adjusted in a stepwise fashion to reach blood glucose levels above 2.6 mmol/L in the first 72 hours of life or above 3.3 mmol/L after 72 hours of life. Blood glucose levels should be monitored 30 minutes after any change in therapy.

In the first 72 hours of life, breastfeeding can be continued without risk of over-hydration, because the volume of colostrum is small. In supplemented infants, in order to avoid dilutional hyponatremia, total oral and IV intake should not exceed 100mL/kg/day. In addition, it is important to carefully monitor electrolytes in these babies.

Q: When should you consider using pharmacological treatments and/or referring to a specialist?

If a glucose infusion rate of over 10 to 12 mg/kg/min is needed to maintain appropriate blood glucose levels, further investigations should be performed in order to identify a possible endocrine pathology or inborn error of metabolism. Generally, referral to endocrinology and investigation for cause of persistent hypoglycaemia should be delayed until the infant is 72 hours old.

Pharmacological intervention in the form of IV glucagon should also be considered if a glucose infusion rate of 10 to 12 mg/kg/min is not sufficient to maintain adequate blood glucose levels. If glucagon is used, it should be given either by IV bolus at 0.1-0.3 mg/kg or by infusion at 10-30 ug/kg/h. Alternative pharmacological therapies include hydrocortisone, diazoxide and octreotide, however, there is limited data to support their use for initial management of hypoglycaemia.

Q: How should infants with persistent hypoglycaemia be treated?

After the transition period, when an infant is over 72 hours old, the therapeutic blood glucose target is >3.3 mmol/L. In infants with persistent hypoglycaemia, a blood glucose level below 2.8 mmol/L should prompt further investigation, with a critical sample. A critical sample is a panel of blood tests to find the cause of persistent hypoglycaemia and must be collected while the infant is hypoglycaemia. The critical sample includes a confirmatory plasma glucose, beta-hydroxybutyrate, bicarbonate, lactate, free fatty acids, insulin, growth hormone, cortisol, carnitine, and acylcarnitine profiling.

For neonates being monitored for persistent hypoglycaemia, precautions should be taken before discharge from hospital. These infants should have a 5-6 hour fast before discharge, with blood glucose levels above 3.3 mmol/L 4-5 hours post-feed, to ensure their safety at home. In addition, an underlying cause of their hypoglycaemia should be determined, and specific medical management should be initiated. It is important to counsel parents about frequency of feeding, glucose monitoring, signs of hypoglycaemia, and treatments for hypoglycaemia, including medications if necessary.

Conclusion: Return to clinical case

Now, back to baby Rachel's case! Rachel is the infant of a gestational diabetic mother, a major risk factor for developing neonatal hypoglycaemia. Therefore, her blood glucose

level was checked at 2 hours of age. You examine Rachel and note that she does not exhibit any signs or symptoms of hypoglycaemia. Because Rachel's glucose level was 2.2 mmol/L, which is below the cut-off of 2.6mmol/L, and she is asymptomatic, you give her a dose of 40% dextrose gel and encourage Rachel's mother to breastfeed her on demand. You recheck her blood glucose level 30 minutes later, and find it has increased to 2.9 mmol/L. You continue to check Rachel's blood glucose levels every 3 hours, prior to feeds, until she is 12 hours old. Her glucose levels remain stable and she is discharged the following morning!

Review main learning objectives

Thank you for listening to this PedsCases CPS podcast on neonatal hypoglycaemia! Let's review our main learning objectives. You should now be able to:

1. Recognize which infants are at risk for neonatal hypoglycaemia
2. Know how to diagnose transitional and persistent neonatal hypoglycaemia
3. Know the signs and symptoms of neonatal hypoglycaemia
4. Recognize which infants should be screened for neonatal hypoglycaemia and know how screening should be performed
5. Know how to manage transitional and persistent neonatal hypoglycaemia

Take away points

1. The most important risk factors for neonatal hypoglycaemia are being small for gestational age, large for gestational age, intrauterine growth restriction, being born prematurely, and being the infant of a mother with gestational diabetes.
2. Transition-related hypoglycaemia is defined as blood glucose levels below 2.6 mmol/L in the first 72 hours of life, and persistent hypoglycaemia is defined as blood glucose levels below 3.3 mmol/L after 72 hours of age.
3. There are two main categories of symptoms of neonatal hypoglycaemia. The neurogenic symptoms include jitteriness, pallor, temperature instability, irritability, and tachycardia. The neuroglycopenic symptoms include apneic episodes, episodes of cyanosis, hypotonia, unresponsiveness, lethargy, seizures, a weak or high-pitched cry, and coma that may lead to death if the hypoglycaemia is not corrected.
4. Infants should be tested for neonatal hypoglycaemia immediately if they are symptomatic or unwell. Infants with risk factors for neonatal hypoglycaemia should be screened at 2 hours of age and every 3-6 hours after that, prior to feeds. Testing can be discontinued after 12 hours of age if LGA or infant of diabetic mother, or 24 hours if SGA, IUGR, or preterm, if blood glucose levels remain >2.6 mmol/L.
5. For asymptomatic infants with blood glucose levels under 2.6 mmol/L, initial treatment should include increased frequency of feeding and supplementation with 40% dextrose gel along with a feed. Alternatively, a measured volume of 5 ml/kg of feed along with breastfeeding may be offered. If this is not successful in raising blood glucose levels, IV dextrose therapy should be considered. For infants with symptomatic hypoglycaemia, IV dextrose therapy should be initiated

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immediately. If IV dextrose therapy is not successful, other pharmacological intervention may be necessary.

6. Infants with persistent hypoglycaemia beyond 72 hours of age should be investigated further when glucose levels are <2.8 mmol/L and should have a therapeutic target of >3.3 mmol/L. Before discharge from hospital, they should maintain blood glucose levels >3.3 mmol/L after a 4-5 hour fast, to ensure safety at home.

We hope that this PedsCases CPS podcast has been helpful. Stay tuned for more podcasts, and thanks for listening!

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