

PedsCases Podcast Scripts

This is a text version of a podcast from PedsCases.com on “**Hypoxic Ischemic Encephalopathy.**” 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.pedsCases.com/podcasts.

Hypoxic Ischemic Encephalopathy

Developed by Carina Lauzon and Dr. Marc-Antoine Landry for PedsCases.com.
August 15, 2018.

Introduction

Hi everyone, my name is Carina Lauzon and I am a third year medical student at the University of Alberta. This PedsCases podcast is designed to give an organized approach to Hypoxic Ischemic Encephalopathy, the leading cause of death or severe impairment in infants, worldwide. This podcast was created with Dr. Marc-Antoine Landry, a neonatologist at the Royal Alexandra Hospital in Edmonton, Alberta, Canada.

Clinical Case

Let’s start with a clinical case: you are a third year medical student working on your pediatrics rotation. During your evening shift, you are called for an emergency Caesarean section for a term baby who has persistent fetal bradycardia. At the time of delivery, the obstetric team told the pediatric team that there was a placental abruption. The baby is born flat, is cyanotic, and is not breathing. The resuscitation team initiates positive pressure ventilation, and despite a good technique, no heart sounds are heard. The team inserts a breathing tube and starts chest compressions. After one minute of CPR there are still no heart sounds. They give epinephrine into the breathing tube and resume CPR. After three minutes, some faint heart sounds are heard. A second dose of epinephrine is given in an umbilical venous catheter that was urgently inserted. Two minutes later, a heart rate is recorded and the team is able to stop chest compressions, the heart rate steadily increases above 100. As the baby is still not breathing, a mechanical ventilator is attached to the breathing tube to ventilate and oxygenate the baby. Considering what you know about this patient, what should your next steps be in terms of brain protection? We will review the answer to this case at the end of the podcast.

Learning Objectives

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

1. Describe the phases of brain injury in hypoxic ischemic encephalopathy.
2. Identify which infants are at risk for hypoxic ischemic encephalopathy.

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3. List the signs and symptoms of hypoxic ischemic encephalopathy.
4. Review the management for hypoxic ischemic encephalopathy.
5. Discuss the prognosis of hypoxic ischemic encephalopathy.

What is HIE?

Hypoxic Ischemic Encephalopathy (HIE) is caused by brain injury that occurs due to impairment of oxygen delivery (hypoxia) and blood perfusion (ischemia) to the brain. This happens as a result of an impairment of the exchange of oxygen and carbon dioxide, which leads to hypoxia, hypercapnia, metabolic acidosis, and other acute nutrient deficiencies. HIE is the leading cause of death or severe impairment, including epilepsy, cerebral palsy, neurodevelopmental delay, and cognitive impairment, in infants worldwide.

In HIE, injury to the brain occurs in two phases, known as the primary and secondary phases. The primary phase refers to the hypoxic ischemic injury itself. Reduction in blood flow and oxygen supply to the brain leads to several biochemical changes, including a fall in ATP, failure of the sodium potassium pump, depolarization of cells, lactic acidosis, release of excitatory amino acids, calcium entry into cell and, if severe, cell necrosis. Following resuscitation and reperfusion, the brain enters into a latent stage, in which we see normalization of oxidative metabolism. However, the infant is still at risk for further damage due to HIE.

The secondary phase of brain injury due to HIE is perhaps more significant than the first, and it is on this phase that current treatment regimens are focused. The secondary phase begins 12-36 hours after injury and may last up to 14 days without treatment. During this phase, apoptosis, mitochondrial failure, cytotoxic edema, accumulation of excitatory amino acids, and release of free radicals, terminating in cell death, are observed. Experimental studies in sheep have shown that a single “sub-threshold” insult during labour, which may cause minor or no neuronal damage in the primary phase, is capable of causing significant injury in the secondary phase.

Risk factors/Causes of HIE

HIE is caused by reduced blood and oxygen delivery to the brain and therefore, anything that causes this is a risk factor for HIE. The main categories of risk factors for HIE include umbilical cord issues, placental complications, and birth complications.

Because the umbilical cord is the fetus’ only source of oxygen and nutrients, its function is critical. Occlusion or compression of the umbilical cord decreases the amount of blood flow to the fetus. This can happen as a result of many factors, such as prolapse of the cord, nuchal cord (cord wrapped around baby’s neck), knotted cord, and infection or inflammation of the cord. Oligohydramnios and polyhydramnios are additional risk factors for umbilical cord compression.

The umbilical cord exchanges blood between the mother and fetus via the placenta, and therefore, placental complications can also lead to decreased oxygen

supply to the fetus. Placental complications that are associated with HIE include placental abruption, ruptured vasa previa, and preeclampsia. Maternal hypotension can result in decreased placental perfusion and thus, decreased delivery of blood to the fetus, and can occur for a variety of reasons, including infection, intrapartum haemorrhage, and uterine rupture.

Finally, complications that occur during and around the time of birth are a risk factor for HIE. These include birth injury due to cephalopelvic disproportion, shoulder dystocia, and improper use of forceps or vacuum extractor during delivery. Additionally, any condition that has the potential to block the baby's airways or impair the lungs' or heart's function for an extended period of time may lead to decreased oxygenation and perfusion of the brain after birth.

Signs and Symptoms

The clinical presentation of HIE depends on the severity of the insult. HIE can be grouped into three categories of symptoms: mild, moderate, or severe.

Mild signs and symptoms include hyperalertness, tachycardia, mydriasis, and a weak suck reflex. Tone is normal or increased, stretch reflexes are overactive, and segmental myoclonus is present. There are no seizures.

Moderate signs and symptoms of HIE include lethargy, hypotonia, bradycardia, periodic respirations, and weak primitive reflexes. Overactive stretch reflexes, segmental myoclonus, and miosis are also seen, and seizures are commonly present.

In severe HIE, signs and symptoms include stupor or coma, flaccidness, absent primitive reflexes, and apnea. Seizures are less commonly present than in moderate HIE.

Treatment

The mainstay of treatment for HIE is therapeutic cooling. Achieving therapeutic hypothermia to a rectal temperature between 33 and 34 degrees Celsius prevents delayed cell death in the secondary phase of HIE and decreases mortality and long term neurodevelopmental disabilities in term infants. The number needed to treat is 7 for the combined outcome of death and major neurodevelopmental disability. Cooling has a broad inhibitory effect on a variety of harmful cell processes that occur during the secondary phase of HIE. Its effects include decreased apoptosis, decreased loss of high-energy phosphate, reduced oxygen consumption, reduced release of nitric oxide, glutamate, free radicals and excitatory amino acid neurotransmitters, and the induction of genes that reduce neuronal death.

Cooling should be initiated as soon as possible, within the first 6 hours of life in infants with HIE, and the optimal duration of cooling is 72 hours. There is a small study

which suggests that infants who are cooled within 3 hours of birth have significantly better motor outcomes than those who commence cooling between 3 and 6 hours of life. In order to be a candidate for cooling, an infant must be less than 6 hours old, greater than or equal to 35 weeks gestational age, and must meet criteria A and B and, in some centres, criteria C.

Criteria A refers to evidence of a metabolic hypoxic-ischemic etiology and is defined in most studies by at least one of the following: APGAR score under 5 at 10 minutes of age, continued need for resuscitation (which includes endotracheal or mask ventilation) at 10 minutes of age, or metabolic acidosis with pH under 7 or base deficit over 16mmol/L in cord or arterial blood within one hour of birth. Criteria B refers to evidence of a clinical neurological exam that shows that the infant has moderate or severe encephalopathy. This is demonstrated by an altered state of consciousness plus at least one of the following: hypotonia or hypertonia, abnormal reflexes including oculomotor or pupillary abnormalities, absent or weak suck reflex, or clinical seizures. Criteria C refers to evidence of abnormal brain activity, defined as clinical seizures or abnormal amplitude integrated EEG.

Cooling can be accomplished via passive and/or active cooling. During the resuscitation of a baby who is suspected to have been exposed to a hypoxic-ischemic insult, the recommendation is to not actively warm the baby. For infants who need to be transferred to another hospital for cooling, passive cooling can be initiated during transport. This is achieved by turning off external heating devices and not warming the baby. When using passive cooling, it is important to continuously measure rectal temperature, so as to avoid temperature oscillations and over or under cooling. Active cooling can be achieved via selective head cooling, using a cooling cap, or total body cooling, using cool packs and cooling blankets. Clinical trials show similar outcomes between these two methods. In practice, total body cooling is used more commonly, as it is cheaper, more likely to be available, and easier to use. In addition, cooling caps carry the risks of scalp edema and skin breakdown.

Mild hypothermia is safe, but there have been some mild side effects described, including bradycardia, arrhythmias, thrombocytopenia, and mild hypotension. Contraindications to cooling include severe head trauma, intracranial bleeding, major congenital anomalies, and congenital abnormalities suggestive of chromosomal anomaly or other syndromes that include brain dysgenesis. In addition, there is currently no evidence regarding the safety or efficacy of cooling in infants born at less than 35 weeks gestational age.

After 72 hours of therapeutic hypothermia, the infant should be rewarmed. When rewarming, it is important to increase the temperature slowly, about 0.5 degrees Celsius every hour, as rapid rewarming puts the infant at a greater risk for seizures.

In addition to therapeutic cooling, management of HIE includes avoidance of hyper and hypoglycemia, as both are associated with death and long-term disability at

18 months of age in infants with moderate to severe HIE. For all term infants, resuscitation in room air is preferred over resuscitation with 100% oxygen. This is because the use of high concentrations of oxygen can cause hyperoxia, which can lead to excessive release of oxygen free radicals and aggravation of brain injury.

Research is currently being conducted in an effort to identify agents that may provide synergistic benefit with therapeutic hypothermia in HIE. Small studies have been performed and suggest that agents such as xenon, erythropoietin, melatonin, and stem cell therapy may be beneficial. These agents work via a variety of mechanisms, including reducing neurotransmitter release, anti-inflammatory effects, increasing neurotrophic and anti-apoptotic factors in the brain, and stimulating antioxidant enzymes.

After initial management, all infants with moderate to severe HIE should be enrolled in follow-up programs. These programs may include early assessments at 4-8 months of age, which focus on general health, head growth and motor development, and assessments at 12-24 months of age, which focus on cognitive skills and language development. Preschool assessments are also important, as they can help identify children who would benefit from early education programs.

Prognosis

The prognosis of HIE depends upon the severity of the injury, and the ability to determine the prognosis is hindered by the difficulty in determining the actual severity of the insult. The mortality rate ranges from 0% in mild HIE, to 5% in moderate HIE, to 80% in severe HIE. However, death is often the result of withholding and/or withdrawing care, and is not always the natural progression of the injury in babies with severe HIE. In infants with moderate to severe HIE treated with therapeutic hypothermia, the mortality rate is about 24-38%.

Another important part of prognosis to consider is the child's risk of adverse neurodevelopmental outcomes. In infants who suffer from mild HIE, the rate of adverse neurodevelopmental outcomes does not differ significantly from the general population. In infants with moderate HIE, the rate is about 20-35%, and the risk is higher if seizures are present. In severe HIE, nearly 100% of survivors will have significant impairments. Possible long-term impairments include cognition and developmental delay, learning disabilities, cerebral palsy, blindness, gross motor and coordination problems, epilepsy, deafness, and behavioural problems. In infants with moderate HIE, it is difficult to predict who will suffer from adverse neurodevelopmental outcomes and the severity of impairment sometimes cannot be determined until the child is three to four years old.

Seizures exacerbate neuronal injury by increasing cerebral metabolic demand, triggering the release of excitatory neurotransmitters, and causing cardiorespiratory instability, and therefore their presence is a poor prognostic factor in HIE. In addition, the presence of "burst suppression," abnormalities of background cycling, and the loss

of sleep wake cycling on EEG is associated with a worse outcome. Normal tracing on EEG done at 7 days of age is associated with a favourable outcome. A normal clinical neurological exam on the 7th day of life or at the time of discharge is a very good prognostic factor, with 90-100% normal outcome.

Conclusion/return to case

Let's return to our clinical case. The baby's mother had placental abruption, which we now know is a significant risk factor for Hypoxic Ischemic Encephalopathy in the infant. At 10 minutes of age, the baby's APGAR score was only 2 and he continued to require ventilation. No active warming was done in the resuscitation area.

After completing all assessments and transporting him to the NICU, you determine that he has a moderate HIE and meets all the criteria for therapeutic hypothermia. Total body cooling is actively initiated by 2 hours of age. At 72 hours, you slowly rewarm the baby, who you now know as Jack, increasing the temperature by 0.5 degrees Celsius every hour. Once rewarmed, Jack begins feeding without difficulty and is discharged on day 6 with a completely normal neurological exam. He is enrolled in a follow-up program.

Ten years later, you are working as a paediatrician when a new patient, a 10-year-old boy named Jack comes to see you for an ear infection. Upon meeting with him and his mother, you realize that this is the same Jack you treated as a medical student ten years ago! You learn that he has had no issues at all and performs well at school; Jack is a happy and thriving young boy!

Thank you for listening to this PedsCases podcast on hypoxic ischemic encephalopathy. Here are some key take away points to review.

Take Away Points

1. In HIE, injury to the brain occurs in two phases: the primary and secondary phases. The primary phase refers to the initial period of hypoxia and ischemia, in which damage occurs in the form of necrosis. The secondary phase occurs 12-36 hours after the injury and in this phase, cell death occurs via apoptosis.
2. Risk factors for HIE include anything that decreases oxygen and blood flow to the brain. This includes umbilical cord issues, placental complications, and birth complications.
3. The signs and symptoms of HIE vary between mild, moderate, and severe HIE, but general symptoms include decreased level of consciousness, hypotonia, weak primary reflexes, and seizures.
4. The mainstay of treatment for HIE is therapeutic hypothermia. Infants born at or after 35 weeks gestation who have moderate to severe HIE should be cooled within the first 6 hours of life to a rectal temperature in between 33 and 34

degrees Celsius for a period of 72 hours. Therapeutic hypothermia reduces the damage that occurs during the secondary phase of HIE and thus, decreases mortality and morbidity.

5. The prognosis of HIE ranges from an almost 0% morbidity and mortality rate in mild HIE, to a 80% mortality rate and nearly 100% incidence of adverse neurodevelopmental outcomes in severe HIE. The rate of neurodevelopmental impairment is between 20 and 35% in moderate HIE; however, it is difficult to predict which infants will go on to develop adverse outcomes and the severity of impairment cannot always be determined until the child is three to four years old.

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

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