

#### **PedsCases Podcast Scripts**

This is a text version of a podcast from Pedscases.com on "**Conjugated Hyperbilirubinemia**." These podcasts are designed to give medical students an overview of key topics in pediatrics. The audio versions are accessible on iTunes or at <u>www.pedcases.com/podcasts</u>.

#### **Conjugated Hyperbilirubinemia**

Developed by Jennifer Ng and Dr. Jason Silverman for PedsCases.com. September 28, 2017.

#### Introduction

Hello! My name is Jennifer Ng and I am a third year medical student at the University of Alberta. This podcast was reviewed by Dr. Jason Silverman, a pediatric gastroenterologist and assistant professor at the University of Alberta and the Stollery Children's Hospital in Edmonton.

By the end of this podcast on conjugated hyperbilirubinemia, the listener will be able to:

- 1. Define conjugated hyperbilirubinemia
- 2. Describe the pathophysiology of conjugated hyperbilirubinemia
- 3. List important and common etiologies of conjugated hyperbilirubinemia
- 4. Describe an approach to the diagnosis and management of conjugated hyperbilirubinemia with a focus on biliary atresia

Here we go!

### Case

You are a third-year medical student on your pediatric rotation in the emergency department, and you've been asked to see Mikey, a 4 week-old neonate with persistent jaundice. Being the astute medical student that you are, you know a 4-week history of persistent jaundice is unusual for physiologic jaundice and you bring this up with your preceptor. Your preceptor replies "correct, this would be an unusual presentation for physiologic jaundice. What do you know about conjugated jaundice? How is it defined and how does it present?"

Let's answer these questions together.

### **Definition**

Hyperbilirubinemia is just as it sounds – increased bilirubin in the blood. There are two ways that a diagnosis of conjugated hyperbilirubinemia is established. The first is defined relative to the total serum bilirubin level. What I mean, is that if the total serum



bilirubin is >85 umol/L, conjugated hyperbilirubinemia occurs if conjugated (or direct) bilirubin comprises >20% of that total. The other way conjugated hyperbilirubinemia is defined is if the absolute value of conjugated bilirubin is > 17umol/L in the context of a total serum bilirubin <85 umol/L.

It is very important to ask for both total bilirubin and fractionated bilirubin when a neonate or infant presents with jaundice as this may not be measured automatically, depending on where you are practicing. Without a fractionated bilirubin, conjugated hyperbilirubinemia may be missed. This is important and needs to be emphasized because conjugated hyperbilirubinemia is always pathologic. There is no normal or physiologic explanation for it, so make sure you order the fractionated bilirubin or else you may miss a pathologic condition.

### Incidence

While hyperbilirubinemia is common in neonates, with 60% of newborns visibly jaundiced in the first week of life, conjugated hyperbilirubinemia occurs just once per 2500 live births, which translates to an incidence of roughly 0.04%.

# **Pathophysiology**

Before we discuss the pathophysiology of conjugated hyperbilirubinemia, let's quickly review normal bilirubin metabolism. When red blood cells and their hemoglobin are broken down, heme is catabolised and bilirubin is a product of this. After bilirubin is released, it is bound to albumin and taken to the liver where it is conjugated by the glucuronosyl-transferase enzyme. This conjugation makes the bilirubin water soluble. Conjugated bilirubin is then excreted by the hepatocytes into the bile. The bile then moves through the bile duct into the digestive tract, where it is then excreted and pigments our stool!

Conjugated hyperbilirubinemia is then an issue of reduced bile flow or formation. Somewhere along the line, the bile can't exit the biliary system, and so it builds up and accumulates in the bloodstream.

### **Presentation and Differential Diagnosis**

Aside from a jaundiced appearance with the typical lab values for conjugated hyperbilirubinemia, the clinical presentation varies depending on the underlying cause. When considering the etiology, biliary atresia (BA) is the big, "can't miss" diagnosis. BA isn't the only cause of conjugated hyperbilirubinemia but the other etiologies aren't as common or as time-sensitive to diagnose. Because it is important to have BA at the top of your list for the differential we will break things down to biliary atresia (BA) and non-BA conditions for our discussion.

Biliary atresia refers to a progressive process whereby the extrahepatic bile ducts become fibrotic and narrowed – sometimes to the point of absence. This abnormal



narrowing effectively obstructs bile secretion. BA is responsible for 25-40% of cases of conjugated hyperbilirubinemia in infants. A critical consequence and finding associated with this obstruction is that the stools are pale and relatively colourless because the bile can't get into the GI tract. This is what we call acholic stools, and they are a red flag for biliary atresia. Another common finding is dark urine because the build-up of conjugated, water-soluble bile is excreted by the kidneys. But because BA patients often appear otherwise well, a high clinical suspicion is needed to make the diagnosis while you consider and investigate for the rest of the differential – as we will discuss later.

Before we move on, there are a few obstructive extrahepatic conditions that can have a similar well-appearing clinical presentation like BA that I should mention. These include choledochal cysts, which are cystic outpouchings of the bile duct that can obstruct flow, as well as common bile duct stenosis, gall stones, and biliary hypoplasia, among others.

So far, we've discussed extrahepatic causes of conjugated hyperbilirubinemia – but what about inside the liver? Not only are there intrahepatic causes of neonatal cholestasis, but systemic diseases can present with conjugated hyperbilirubinemia as well!

Infections account for 5% of cases of conjugated hyperbilirubinemia in infants with the common culprits being congenital infections (such as the TORCH infections) as well as HIV, hepatitis B, adenovirus, parvovirus B19, coxsackie virus as well as UTIs or neonatal sepsis in general. In addition to being jaundiced, these babes can appear quite ill and may present with non-specific symptoms or infectious symptoms such as irritability, poor feeding, vomiting, diarrhea, lethargy, or oliguria. In contrast however, even an otherwise asymptomatic UTI can be associated with cholestasis.

Inborn errors of metabolism make up roughly 20% of neonatal cholestasis patients and these conditions include galactosemia, hereditary fructose intolerance, tyrosinemia, neonatal Dubin-Johnson among others. Cholestasis may also be due to genetic conditions. For instance, alpha-1-antitryspin deficiency accounts for 10% of these babes, but other genetic conditions such as CF, trisomies 13, 18, and 21, progressive familial intrahepatic cholestasis, and Alagille syndrome can also be responsible. Alagille syndrome is an interesting condition whereby there is a paucity of bile ducts within the liver.

The broad differential for neonatal cholestasis also includes immune-mediated disease (such as GALD (gestational alloimmune liver disease), formerly known as neonatal hemochromatosis), and systemic diseases (including hypopituitarism, hypothyroidism, neonatal lupus erythematous, and heart failure). In the case of a systemic disease, you would expect to see other manifestations of that disease process. And finally, idiopathic neonatal hepatitis accounts for the remainder of neonatal cholestasis.

Now that we know the definition of conjugated hyperbilirubinemia, its pathophysiology and key conditions in its broad differential, let's return to our case.



# Case

When you go to see Mikey, his parents tell you that 1 week ago, he started to look yellow, starting with his eyes and then eventually his skin. Mikey is formula fed, but his parents haven't noticed any improvement in his colour despite changing his formula – as suggested by his family physician. When you ask about stool colour, they report that it's been "white as eggshells" for the past week, and his urine has been quite dark as well. They report that Mikey has otherwise been well with no fevers, nausea, or vomiting – and he's been feeding well too.

Mikey was born at 38weeks and 2 days via spontaneous vaginal delivery, and there were no complications with the pregnancy or his birth – and he was discharged home the next day with no NICU stay or any concerns. Birthweight was 3.5 kg. He's been followed by his family physician with regular visits and did not appear jaundiced early on. When asked specifically, Mikey's parents say that he has had the standard newborn metabolic screen, which was normal.

On exam, Mikey's is afebrile, and his vitals are normal for age, and he is alert and in no distress. His weight is at the 50<sup>th</sup> percentile. He is jaundiced from head to toe, but most markedly on his head and his eyes. His abdomen is soft and nontender. Palpation of his liver shows slight hepatomegaly. There is no splenomegaly. The remainder of his exam is unremarkable.

When asked, his parents show you his most recent diaper and you see an stool that appears very pale or "clay" coloured, which his parents report is consistent with his stools for the past week.

Preliminary bloodwork is consistent with conjugated hyperbilirubinemia. His total bilirubin is elevated at 98umol/L, with a conjugated bilirubin of 40umol/L (41% of total). ALT and AST are both slightly elevated at 54 units/L and 66 units/L, and ALP is 430 units/L. These results are suggestive of a cholestatic process. You send off his urine, and urinalysis comes back unremarkable with no bacteria seen.

With a confirmed conjugated hyperbilirubinemia and some concerning features, your clinical suspicion for biliary atresia is high. But how do you distinguish biliary atresia from other causes of conjugated hyperbilirubinemia? How would you manage it?

Before we answer these questions, let's explore why biliary atresia is such a time sensitive diagnosis.

### **Diagnosis and Management**

The only effective treatment for biliary atresia is surgical intervention – specifically the hepatoportoenterostomy (or Kasai) procedure. With the Kasai procedure, the fibrotic and narrowed parts of the extrahepatic bile duct (+/- the gallbladder if it is fibrotic) are removed as upstream and deep into the liver as necessary to get satisfactory bile flow –



this can sometimes require resection of intrahepatic parts of the bile duct. The remainder of the ductal system that has good bile flow is then connected directly to the GI tract. The reason that BA needs to be diagnosed quickly is that the Kasai procedure is most successful when done in the first 60 days of life. As described earlier, biliary atresia is a progressive disease. Therefore, earlier intervention is more favourable because the fibrosis and narrowing of the ducts is less severe and more salvageable earlier on in the disease. On the flipside, without intervention, complications such as liver cirrhosis, liver failure, portal hypertension can occur, with death being the eventual outcome. But even with a successful Kasai procedure, 75% of patients will need a liver transplant before the age of 20 and as many as 50% will need a transplant in the first 2 years after surgery.

So now that we understand the importance of diagnosing and treating biliary atresia early on, how do we go about distinguishing BA as a cause of conjugated hyperbilirubinemia versus, say, Alagille syndrome? Pinning down the cause of neonatal cholestasis requires a variety of labs, imaging, and biopsies under the guidance of a working diagnosis.

When these neonates first present to primary care, the first and foremost thing to start with is a thorough history and physical examination. This can help you establish if the infant is well or unwell, and whether they have any concerning symptoms or physical exam findings that might suggest an acute or systemic illness. Accordingly, the initial workup should be for infectious, systemic and metabolic causes – especially if they appear unwell. Similarly, a baseline liver panel should be done, including: liver enzymes comprised of total and conjugated bilirubin, ALT, AST, ALP, GGT, and markers of liver function including INR, glucose, albumin and ammonia to assess liver disease and severity. It is also critical to assess for acholic stools – either direct observation, or from photos, because this will point towards a more anatomic/obstructive cause such as BA or choledochal cyst. Another quick, non-invasive way to assess for visible obstructions in the biliary tree is to do an abdominal ultrasound.

When the more common treatable disorders are ruled out and the severity of liver disease is established, it is helpful to consult a pediatric gastroenterologist or hepatologist for further guidance with respect to etiology specific investigations (although consultation may be helpful at any point in this process). The assessment for complex and rare conditions goes beyond the scope of this podcast, but these could include specific metabolic, infectious, and genetic markers. Similarly, targeted investigations may be done to assess for systemic disease as well – such as a TSH for thyroid disease, and a sweat chloride test for CF.

When the suspicion for biliary atresia is high, you need to do a liver biopsy. The liver biopsy is highly sensitive and specific for BA and it is the key test in the workup of neonates with neonatal cholestasis. If interpreted by an experienced pathologist, a liver biopsy can correctly diagnose BA 90-95% of the time, which is helpful to avoid unnecessary surgery. Ultimately, the gold-standard diagnostic test for biliary atresia is



an intraoperative cholangiogram and histological exam of the bile duct remnant, but by this time the patient is already in the OR, ready to have the Kasai procedure done.

To wrap things up, following the Kasai procedure, the patient needs to be followed up regularly to monitor their liver function, and to assess if a liver transplant is necessary. As for management of non-BA causes of conjugated hyperbilirubinemia, the treatment is etiology specific and we won't delve into these for the purpose of this podcast.

### Case

Now back to the case. Mikey is admitted and a liver biopsy is sent off. The biopsy comes back consistent with biliary atresia and so Mikey is booked for a Kasai procedure the follow day. A pediatric gastroenterologist will follow Mikey in the coming months and years to assess the success of his Kasai procedure and if he will need a liver transplant.

Before we finish off, let's revisit the learning objectives and some take home points.

### Learning Objectives

- 1. Define conjugated hyperbilirubinemia
- 2. Describe the pathophysiology of conjugated hyperbilirubinemia
- 3. List important and common etiologies of conjugated hyperbilirubinemia
- 4. Describe an approach to the diagnosis and management of conjugated hyperbilirubinemia with a focus on biliary atresia

# Take-Home Points

- 1. Conjugated hyperbilirubinemia is always pathologic
- 2. Jaundice beyond 4 weeks of life MUST be evaluated for the possibility of conjugated hyperbilirubinemia.
- 3. Always check for acholic stools whether that's seeing them directly or through photos
- 4. While biliary atresia patients often appear "well", BA is a time sensitive diagnosis because the Kasai procedure is most successful in the first 60 days of life.
- 5. Keep your differential broad because biliary atresia is not the only cause of neonatal cholestasis

# **References**

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