PedsCases Podcast Scripts

This podcast can be accessed at www.pedscases.com, Apple Podcasting, Spotify, or your favourite podcasting app.

Alagille Syndrome

Developed by Michelle Choi and Dr. Kerry Wong for PedsCases.com.
November 14, 2024

Introduction

Hi everyone! I am Michelle Choi, a second year medical student from the University of Alberta. This podcast was completed in collaboration with Dr. Kerry Wong, a pediatric gastroenterologist with a specialization in hepatology at the Stollery Children's Hospital in Edmonton, Alberta.

Learning Objectives

By the end of this podcast, listeners will be able to:

1. List the initial workup for infants presenting with neonatal jaundice
2. Describe an approach to the diagnosis of Alagille syndrome
3. Identify and discuss the genetic basis of Alagille syndrome
4. Review the clinical presentation of Alagille syndrome in infants
5. Describe the approach to management of a child with Alagille syndrome

To meet our learning objectives, let's walk through a clinical case. You are a clerkship student on your pediatric rotation, and you have been asked to see Heather, a 4 month old infant brought into the clinic by her mother, Samantha. Heather's chart denotes that her mother is worried about some yellowing in the whites of Heather's eyes and in her skin, as well as poor growth. Your preceptor asks you to see Heather and take a detailed history as well as perform a physical exam.

History/Physical Exam

Before we see Heather, let's first discuss some key points to consider during your history taking. As always, it is important to take a detailed history that includes the patient's identification, chief complaint, history of presenting illness, past medical history, family history, prenatal course, birth history, immunizations, nutrition and development.

For infants presenting with yellowing of the sclera, skin and mucous membranes, also known as jaundice (1), there is some key information we want to extract to help us with our differential. This information will help us determine if the infant's jaundice is physiologic or pathologic. It is important to specifically note whether there was jaundice present in the newborn period, if there is consanguinity in the family, or neonatal jaundice or cholestasis in parents or siblings (2).

Developed by Michelle Choi and Dr. Kerry Wong for PedsCases.com.
November 14, 2024.

Some important history points in the birth history include the mother's prenatal history. This includes any prenatal ultrasound findings, if there was cholestasis of pregnancy, if there was acute fatty liver of pregnancy and/or maternal infections (2). With the infant birth history, it is important to find out the gestational age at birth, whether the infant was small for gestational age, any results from newborn screening and whether there were any pre or perinatal infections for the mother or baby (2). It is also important to make note of the infant's source of nutrition, whether it is breast milk or formula, as well as if there have been any growth, vision, or hearing concerns (2). You should also ask about the status of the infant's stool and urine, specifically the colour, and if there has been any recent vomiting (2).

In terms of the physical exam, it is important to note any differences in the patient's general appearance, if there is enlargement of the liver or spleen, any heart murmurs, and on direct inspection, the characteristics of their stool (2). Plotting the patient on a growth chart is also critical (3).

So let's get back to the case. You take a detailed history and perform a physical exam. You learn that Samantha noticed Heather's yellow appearance one month ago. She was not jaundiced during the newborn period. She also explains that she is concerned about Samantha's growth, as she has only gained 350g since birth. From the family history, you learn that Samantha has type 2 diabetes and hypertension, and Heather's dad Bill, has anxiety as well as Alagille syndrome. You make note of this because you remember Alagille syndrome is a genetic cause of cholestatic jaundice (2).

On inspection, Heather does have yellowing in her sclera as well as yellow skin from head to toe, suggesting jaundice. On palpation, you feel some hepatomegaly. There is no splenomegaly. You then auscultate to listen to Heather's lungs and heart. Lungs sound normal, with equal air entry to both lung bases, however you did notice a whooshing murmur sound when listening to Heather's heart. Finally, after checking Heather's diaper for her stool, you notice her stool looks hypopigmented. Based on your findings and Heather's history, you discuss with your preceptor that Heather's persistent jaundice, poor growth, hepatomegaly and hypopigmented stools indicate evaluation of cholestasis (2) and your preceptor discusses the appropriate blood tests.

Initial Workup

So let's review what the blood test should include. It should include a CBC with differential, electrolytes, blood urea nitrogen and creatinine (2). It should also include conjugated bilirubin and total bilirubin to discriminate conjugated vs unconjugated hyperbilirubinemia (2). As well, alanine aminotransferase (ALT) and aspartate aminotransferase (AST) tell us about hepatocyte injury, gamma-glutamyl transferase (GGT) and alkaline phosphatase (ALP) tell us about biliary injury or obstruction, and international normalized ratio (INR) and albumin assess hepatic function (2).

Conjugated bilirubin comes back at 120 umol/L which is significantly elevated, ALT and AST are elevated at 90U/L and 100U/L respectively, and GGT is elevated as well at 120U/L. These results suggest a cholestatic process and prompt further investigation of the cause. For

additional learning, please listen to our “Conjugated Hyperbilirubinemia” podcast, developed by Jennifer Ng and Dr. Jason Silverman.

Differential Diagnosis

Now that Heather’s cholestasis is confirmed, let’s go through some potential causes of cholestasis. The etiology’s can be divided into extrahepatic, hepatocellular and multisystem diseases (2). Let’s first discuss a couple potential extrahepatic causes of Heather’s cholestasis. The most important extrahepatic diagnosis to remember is biliary atresia, as it is the most common cause of cholestatic liver disease in infants and is a “can’t miss” diagnosis (2). This is because surgical treatment outcomes are optimal when the baby is less than 60 days of age (2). Although Heather has a family history of Alagille syndrome, we will first need to rule out biliary atresia in our initial workup. Another extrahepatic cause of cholestasis could be choledochal cysts (2). Some hepatocellular diseases that could result in cholestasis include an alpha-1-antitrypsin deficiency and idiopathic neonatal hepatitis syndrome (2). Finally, possible multi system diseases resulting in cholestasis include Alagille syndrome and cystic fibrosis (2).

Additional Investigations

At this point, it is important to consult pediatric gastroenterology. Under direction of the pediatric gastroenterologist, Heather is admitted for ongoing assessment and management. The GI team orders an abdominal ultrasound to evaluate for biliary atresia, and genetic testing to investigate the family history of Alagille syndrome. Cardiology is also consulted for an echocardiogram to investigate the murmur you heard on physical exam. Ophthalmology is consulted to examine Heather’s eyes for anomalies associated with Alagille syndrome.

While genetic testing results have not come back yet, we have some results to review. There are no signs of biliary atresia from the abdominal ultrasound, as there is presence of a normal gallbladder (4), as well as no signs of choledochal cysts. The cardiologist has determined she has peripheral pulmonary stenosis visible on echocardiogram. There is also a posterior embryotoxon found from ophthalmic examinations. So what does this mean? Do these findings meet the diagnostic criteria for Alagille syndrome?

Diagnosis

Well, let’s first discuss how Alagille syndrome is diagnosed! Genetic testing should be employed to diagnose Alagille syndrome (5). Alagille syndrome is an autosomal dominant genetic disorder with a JAG1 or NOTCH2 mutation in the Notch signaling pathway (5). More than 90% of patients with clinical Alagille syndrome have a mutation in JAG1, about 1% have a mutation in NOTCH2, and although very rare, some individuals with a confident clinical diagnosis of Alagille syndrome, do not have any variants in JAG1 or NOTCH2 (5).

However, it is still possible to diagnose Alagille syndrome clinically as genetic testing is not always available. Before we discuss the criteria of diagnosing Alagille syndrome clinically, let’s discuss what the typical clinical presentation of infants with Alagille syndrome is.

Clinical Presentation

The majority of patients will present within the first 3 months of life (5). Symptoms and manifestations of Alagille syndrome can vary between individuals, but typical presentation includes liver involvement (5). This can manifest as cholestasis which can lead to noticeable jaundice, pruritus, xanthomas, a fat soluble vitamin deficiency, malnutrition, growth failure, and/or cirrhosis with portal hypertension (5). Liver involvement is seen in the majority of cases of Alagille syndrome (5).

In up to 90% of Alagille syndrome cases, there is an associated congenital heart defect (3). Most commonly peripheral pulmonary stenosis in ⅔ of cases, where the pulmonary arteries are narrowed (3). Other defects include tetralogy of Fallot, patent ductus arteriosus, septal defects and coarctation of the aorta (3).

There are skeletal abnormalities including butterfly vertebrae, which is the most common in 70% of cases (3). There may also be temporal bone abnormalities, middle ear bone defects, metabolic bone disease, osteopenia and fractures (5).

There are also ocular anomalies, most commonly the posterior embryotoxon in up to 89% of cases, which is characterized by a prominent Schwalbe ring (3). Other anomalies include optic disc drusen and hypopigmentation of the peripheral retina (5).

In Alagille syndrome, there are also some characteristic facial features (3). These include a prominent forehead, deep set eyes with moderate hypertelorism, a pointed chin and a saddle or straight nose with a bulbous tip (6). These features combined give the face an inverted triangular look (6). This may not always be noticeable and is hard to observe in infants.

There is also renal involvement in 23 to 74% of cases where renal dysplasia is the most common (3). Renal tubular acidosis, vesicoureteric reflux, urinary obstruction and glomerular mesangiolipidosis may also be present (5).

More than half of patients with Alagille syndrome have growth failure, although this is multifactorial (3). There are specific Alagille growth charts which the patient can be plotted on (3).

Lastly, patients with Alagille syndrome may have developmental delays (3). Patients should be assessed and supported by a multidisciplinary team to identify and support any challenges (3). They may also experience impaired quality of life and mental health issues due to severe pruritus (7).

Now that you have an idea of the clinical picture of a patient with Alagille syndrome, you can apply your knowledge to diagnose it clinically using the following criteria, if genetic testing is unavailable or you are waiting on the results to return. To diagnose Alagille syndrome clinically without genetic testing, a patient should have syndromic paucity of the interlobular bile ducts, and 3 or 4 of the following criteria (5):

1. Cholestasis
2. Evidence of cardiac disease

Developed by Michelle Choi and Dr. Kerry Wong for PedsCases.com.
November 14, 2024.

3. Skeletal abnormalities
4. Ocular anomalies
5. Characteristic facial features
6. Renal involvement
7. Vascular involvement

However, if the patient has a first degree relative with a definitive diagnosis of Alagille syndrome, then only 1 or 2 of these additional criteria need to be met (5). Heather meets the criteria for a clinical diagnosis of Alagille syndrome.

A few weeks later, genetic testing results come back and it is confirmed that Heather has a JAG1 mutation. So now that Heather has been diagnosed genetically and clinically with Alagille syndrome, both Samantha and Bill come to discuss the diagnosis and management plan.

Management

Management of Alagille syndrome depends on the presenting signs and symptoms of the patient and consideration of conditions associated with the syndrome (3). These investigations may include an ECG, an echocardiogram, an xray of the spine, an ophthalmologic evaluation, renal ultrasound, and nutritional/growth and developmental assessment (3). It may also be necessary to do a brain MRI/MR angiography in order to evaluate vascular anomalies (3).

In patients with liver symptoms and good synthetic function, the medication, Ursodiol (UCDA) can be used to treat cholestasis by increasing bile flow from the liver to small intestine (5). To combat pruritus, which can significantly negatively impact a patient's quality of life, there are local cutaneous therapies including avoidance of drying soap and administration of ointments (5). It can be helpful to involve a dermatologist (3). Ursodeoxycholic acid (UDCA) may also help with pruritus (3). If pruritus does not improve with UDCA, antihistamines can be given (3). However, make sure to consider daytime drowsiness when suggesting certain antihistamines (3). If pruritus is still not resolved, rifampin can be added to try and decrease itching (5). Unfortunately, none of these therapies are extremely effective.

Recently, new medications called ileal bile acid transport (IBAT) inhibitors have been approved for use in Canada (7). These medications block bile acid uptake at the enterocyte level and the bile acids are excreted in stool (3). Maralixibat is an oral medication that can be given to patients 1 year of age or older and has been shown to significantly reduce pruritus (7).

In a patient with ongoing poor synthetic function, liver transplant after preoperative assessment of cardiac and renal disease, is indicated (5).

In patients with cardiac and renal anomalies, coordination and collaboration with the cardiac and renal teams is critical to support overall health and the optimal timing of interventions (5).

To address malnutrition, it is important to involve a dietitian (3). Patients may need fat soluble vitamin supplementation, formula composed of medium chain triglycerides, or for severely affected infants, a nasogastric tube for enteral feeds (6).

Developed by Michelle Choi and Dr. Kerry Wong for PedsCases.com.
November 14, 2024.

Now back to the case. Investigations are done to evaluate Alagille syndrome associated anomalies and Heather will then receive a management plan based on those results.

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

1. List the initial workup for infants presenting with neonatal jaundice
2. Describe an approach to the diagnosis of Alagille syndrome
3. Identify and discuss the genetic basis of Alagille syndrome
4. Review the clinical presentation of Alagille syndrome in infants
5. Describe the approach to management of a child with Alagille syndrome

Take Home Points

1. In a patient with neonatal cholestasis/conjugated hyperbilirubinemia, you should keep your differential broad but you will want to first exclude biliary atresia.
2. Take a comprehensive history including family history, as it can help point towards potential genetic causes.
3. For all patients with Alagille syndrome, it is important to evaluate associated anomalies and involve a general pediatrician, subspecialists and allied health to support optimal management and health.

This concludes our podcast! Thank you for listening!

References

1.Feldman AG, Sokol RJ. Neonatal Cholestasis. Neoreviews. 2013;14(2):10

2.Fawaz R, Baumann U, Ekong U, Fischler B, Hadzic N, Mack CL, et al. Guideline for the Evaluation of Cholestatic Jaundice in Infants: Joint Recommendations of the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition and the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition. J Pediatr Gastroenterol Nutr. 2017 Jan;64(1):154-168.

3.Krantz ID, Piccoli DA, Spinner NB. Alagille syndrome. Journal of Medical Genetics. 1997;34:152-157.

4.Zhou W, Zhou L. Ultrasound for the Diagnosis of Biliary Atresia: From Conventional Ultrasound to Artificial Intelligence. Diagnostics (Basel). 2021;12(1):51.

5.Kamath BM, Piccoli DA. Alagille Syndrome. In: Murray K, Horslen S, editors. Diseases of the Liver in Children. New York: Springer; 2014. p. 227-246.

6.Turnpenny PD, Ellard S. Alagille syndrome: pathogenesis, diagnosis and management. Eur J Hum Genet. 2012;20(3):251-257.

7.Maralixibat (Livmarli): CADTH Reimbursement Recommendation: Indication: For the treatment of cholestatic pruritus in patients with Alagille syndrome. Ottawa (ON): Canadian Agency for Drugs and Technologies in Health. 2024 May;4(5).

Developed by Michelle Choi and Dr. Kerry Wong for PedsCases.com.
November 14, 2024.