Cystic Fibrosis: Classic Presentation

Developed by Rose Sun, Dr. Tamizan Kherani and Dr. Melinda Solomon for PedsCases.com
October 7, 2021

Introduction:

Hi everyone, welcome back and thank you for listening to part 2 of a series of 2 PedsCases Podcasts on Cystic Fibrosis (CF). In part 1 of this series we looked at the neonatal presentation of CF and newborn screening and in part 2 we are going to cover the classic presentation and acute respiratory exacerbations. My name is Rose Sun and I am a second year Pediatrics resident at the Hospital for Sick Children in Toronto, Ontario Canada.

This podcast was developed with support from Dr. Tamizan Kherani, a pediatric Respirologist and the director of the Cystic Fibrosis program at the Stollery Children's Hospital in Edmonton, Alberta, Canada. As well as Dr. Melinda Solomon, a pediatric Respirologist and the director of the Cystic Fibrosis clinic at the Hospital for Sick Children in Toronto, Ontario Canada.

In the previous podcast, we discussed newborn CF screening, early presentations and diagnostic tests. We also went over in detail the pathophysiology and etiology of CF.

In this second podcast, our learning objectives will be to:

1. Review the common clinical features and complications of CF
2. Discuss the prognosis of CF in children and adolescents
3. Develop an approach to prevent, investigate and manage an acute respiratory exacerbation

In the previous podcast we were introduced to the case of baby Matt, a 2-day-old infant born from an otherwise normal pregnancy and delivery. He presented with low birth weight, failure to thrive, bilious vomiting and poor feeding. At that point he had yet to pass his meconium. There was also a positive family history for cystic fibrosis. The abdominal examination revealed palpable dilated bowel loops and he appeared cachectic. His clinical history and examination were suggestive for bowel obstruction and on imaging he was confirmed to have meconium ileus with dilated bowel loops and meconium impaction. Serial Gastrografin enemas were used to evacuate his bowels. Following the management of the meconium ileus he went on to have a sweat chloride

test, the Gold standard for CF diagnosis. This was positive and he was diagnosed with CF. In this Podcast, we will follow the case of baby Matt into childhood to illustrate the long-term complications, management and prognosis of CF.

Following the diagnosis of CF, it is essential to communicate with the family and inform the child's family physician or pediatrician. CF is a lifelong condition that requires longitudinal cooperation between the family, the local CF team and general practitioners who are also involved in the child's care. It is crucial to establish a trusting and open therapeutic relationship from the beginning.

So let's review the pathophysiology, complications and therapies of CF before we meet with the family.

As mentioned previously, CF is an autosomal recessive condition with mutations in the CFTR gene. CFTR ATP – dependent chloride channels are found in various epithelial tissues in the body. Consequently, CF can affect multiple systems including the lungs, pancreas, gut, liver and reproductive tracts. We will discuss each in detail.

Respiration complications:

We will first look at the respiratory complications including: bacterial infections, allergic bronchopulmonary aspergillosis (ABPA), pneumothorax and nasal polyps. We begin with the most common complication, an increased susceptibility to airway infections. This is due to the lack of functional chloride channels in the lungs leading to reduced chloride secretion and increased sodium chloride absorption. Thus, there is more viscous mucus produced and impaired mucus clearance disrupting the maintenance of a normal airway surface liquid layer. Lack of an adequate airway surface layer prevents proper ciliary clearance of the lungs. In addition, prolonged and persistent airway bacterial colonization can further lead to neutrophil mediated inflammation and subsequent damage to the lung tissue. Frequent and regular cultures of sputum samples or throat swabs are highly recommended. Treatment is very important and heavily influences overall survival. We will talk more about pulmonary exacerbation and bacterial infections later in this podcast.

Another pulmonary complication is allergic bronchopulmonary aspergillosis (ABPA). It is present in up to 30% of children with CF but only causes significant allergic immune response in a third of the case. It can often present with wheeze and productive cough with infiltrates seen on CXR and otherwise unexplained deterioration in lung function. The hypersensitive reaction is IgE mediated; therefore, positive *Aspergillus* skin prick testing and an increased in serum specific IgE supports the diagnosis. Treatment with prednisone and with the possible addition of itraconazole/ voriconazole can prevent progression to bronchiectasis and pulmonary fibrosis.

Despite being relatively rare with only a 1% annual risk in older children, pneumothorax is a life-threatening complication of CF that requires immediate care and admission. A child may present with typical symptoms of chest pain and shortness of breath. Imaging using CXR and/or CT will help in the diagnosis. While small pneumothoraces may resolve spontaneously, large ones will usually require drainage. During this time IV antibiotics may be initiated as lung clearance is reduced.

Finally, nasal polyps can occur in 10-20% of children with CF. They may lead to obstruction or even persistent discharge and post nasal drip. Surgery is usually not performed due to a high rate of reoccurrence and is often well managed with nasal steroid spray.

Gastrointestinal Complications:

Next we will review the gastrointestinal complications of CF with the most important being pancreatic insufficiency. In children with CF up to 90% will have pancreatic duct obstruction due to autolysis of the exocrine duct leading to a loss of function; the lack of pancreatic enzymes lead to insufficient lipase production for fat digestion. This often presents as failure to thrive . Therefore, this is the reason why nutrition along with pancreatic enzyme supplements and fat soluble vitamins are so essential to the growth and well-being of children with CF.

Nutritional status has been strongly associated with pulmonary function and survival in CF. Multidisciplinary expertise with support from a dietician are essential in the care of CF patients. Malnutrition can be further worsened during times of pulmonary exacerbations from increased energy demand and poor appetite. Therefore, monitoring growth by looking at weight increase in proportion to increase in height and BMI are very important. Early intervention is essential to avoid significant loss of weight or linear growth. Dietary intervention can be tried in a stepwise approach. First anticipatory guidance is important with reinforcement of adherence to a diet with sufficient energy intake and pancreatic enzyme replacement in those who have pancreatic insufficiency . Next supplementation with fat powder in milk or high calorie milkshakes orally or through nasograstric (NG) or nasojejunal (NJ) tube feeds may be useful as a time-limited trial. Lastly in severe malnutrition longer term enteral feeding, for example with a Gastrostomy tube (G-tube), may be necessary.

We start enzyme supplementation in all children with a CF diagnosis and signs of malabsorption. In well infants or those picked up on newborn screening their pancreatic status will be assessed by the fecal fat elastase test. As well, it is important to monitor those who are pancreatic sufficient, as a few can become pancreatic insufficient later on. In infants who need enzyme supplementation we can give enteric coated granules of pancreatic enzymes (Creon or Cotazyme). The enzymes are to be taken with all

foods containing fats and at the beginning and during meals. It is not recommended to have an enzyme supplementation dose exceeding 10 000U/kg/day as there have been studies to suggest a possible increase in risk of developing colon fibrosis. It is essential to also supplement and monitor annually the serum levels of fat-soluble vitamins A, D, E and K with blood work, as they may be deficient. Fat soluble vitamin deficiency may present as bleeding problems (vitamin K) fontanelle fullness (vitamin A) and/or hemolytic anemia (vitamin E).

Similar to meconium ileus, which baby Matt initially presented with, distal ileum obstruction can still occur in up to 10% of children with CF after the neonatal period as distal intestinal obstructive syndrome (DIOS). Again, this is due to increased mucus and delayed transit time secondary to steatorrhea. It can often present acutely or chronically as colicky pain possibly associated with eating, abdominal distention and vomiting. Abdominal X-ray may show distention and impacted fecal materials similar to MI. It is important to note that this presentation may be non-specific and other differentials including appendicitis, adhesions from previous procedures, intussusception, volvulus and constipation may need to be ruled out.

CF related diabetes (CFRD) or glucose intolerance has a prevalence of 5-10%. Younger children usually have intact endocrine function; however, by 20-30 years of age CFRD often presents insidiously with weight loss, fatigue and poor appetite rather than the classic presentation of diabetes mellitus of polyuria, and polydipsia. Therefore, it is important for us to detect GFRD early with annual screening with an oral glucose tolerance test (OGTT) in all children with CF over the age of 10.

Furthermore, infants with CF and history of MI like baby Matt, and those with pancreatic insufficiency are at an increased risk for developing neonatal cholestasis. They are also at an increased risk hepatobiliary complications including liver cirrhosis, portal hypertension, gall stones and biliary sludging. Although only 5-10 percent of children develop CF related liver disease (CFRLD) it is a significant cause of morbidity and mortality. Diagnostic evaluation includes clinical examination for stigmata of liver disease along with biochemical evaluation of liver injury and function. Imaging such as doppler ultrasound may be helpful to detect radiographic cirrhosis and signs of portal hypertension. As well, an upper GI scope may be used for diagnosis and intervention if there is concern of portal hypertensive gastropathy. Finally, a liver biopsy will determine the degree of fibrosis and to exclude other potential causes of disease while taking into consideration the risks of the procedure. If the cirrhosis progresses to end stage liver failure, liver transplant may be considered with care at a multidiscipline transplant centre.

Reproductive Tract Complications:

Additionally, reproductive complications of CF can lead to infertility in most males and a smaller portion of females. As well, boys and girls with CF tend to have on average a 2-year delay in the onset of puberty due to poor nutrition and chronic disease. Up to 98% of men with CF are infertile due to bilateral absence of vas deferens and obstructive azoospermia, although sexual performance and libido are preserved. Women can have decreased fertility due to the combination of poor nutrition, anovulation and viscous cervical mucus.

Initial Diagnosis:

So after reviewing most of the common clinical features and complications of CF we will disclose and explain the diagnosis to Matt's parents Kate and John. As you have learned, CF is a systemic disease that affects many organ systems in the body. Usually in the first meeting we should try to be brief and not bombard the family with too much information and instead focus on the most common complications pertaining to the lungs, and pancreas. With regards to the increased susceptibility to airway infections it is important to educate the family about infection control measures. This includes good hygiene, for example proper hand washing, room air ventilation, and cleaning surfaces as most bacterial and viral infections are spread through droplet and direct contact. It is recommended for children with CF to not interact with other children or adults who may be sick. In addition children with CF are not cohorted with other children with CF especially in inpatient settings due to the risk of exchanging pathogens. At this point we may also ask our physiotherapy colleges to provide information to the family about chest physiotherapy. Currently in North America there has been inadequate evidence to suggest the benefit of prophylactic antibiotics; however, in the UK prophylactic floxacin is used until 3 years of age.
For baby Matt's diet, we would recommend breast feeding with supplementation of vitamin A,D,E and K. and continuous monitoring of his weight and height growth. If his mother is unable or elects not to breast feed, he can be given nutrient-dense infant formula. As with all infants and children juice is not recommended. Since baby Matt did not require surgery for his MI, we will monitor him further for signs of poor weight gain, and bowel movements that are loose, large, smelly and contains mucous with bloating prior to the initiation of enzymes.
Kate feels a bit overwhelmed with all this information and you recommend following up soon at the multidisciplinary CF clinic with time especially dedicated to having a discussion with the dietician, nurse and physiotherapist. She pauses for a few seconds and asks you about the survival and long term prognosis of a CF diagnosis. At this point it is crucial to set up appropriate expectations for the prognosis and treatment in that CF is serious and life-shortening conditioning, but also not take away hope for the family. The median age of survival for Canadians with cystic fibrosis is currently estimated to be 52 years of age and increasing with more knowledge about the disease and

advancements in treatments. With good care and outcomes, baby Matt can be expected to go to school and play sports as well.

Novel Therapeutic Agents:

The family ask if there are any new advancements in the treatment. Just in the last few 10 years there have been promising new therapeutic targets for CF that aims to treat the underlying genetic defect rather than the symptoms. As CF is caused by a monogenic defect in the CFTR gene, there is potential for personalized therapies. Gene therapies using viral vectors are currently being studies in human trials, however there has yet to be evidence showing long term restored CFTR expression and function. Chaperones, or aminoglycosides derivatives that aids in intracellular trafficking can work to restore CFTR protein function depending on the class type of the mutation and can potentially correct the dysfunction of the chloride channel. Some specific examples include the 2013 development and approval of Ivacaftor (Kalydeco), a cystic fibrosis transmembrane conductor regulator (CFTR) potentiator. Additionally in recent years combination drugs including Orkambi (lumacaftor and ivacaftor) , Symdeko (tezacaftor and ivacaftor) and Trifakta (elexacaftor /tezacaftor /ivacaftor) are progressing through clinical trials. Lumacaftor, tezacaftor and elexacaftor are corrector modulators which increase the stability of CFTR protein to maximize the effect of ivacaftor. Tezacaftor has been shown to have a better side effect profile as compared to lumacaftor. Elexacaftor is able to correct an additional flaw in the formation of the F508 CFTR protein.
CF treatment has changed significantly in the last decade leading to a substantial increase in the survival and quality of life and there is so much potential for further therapeutics in baby Matt's life time.

Respiratory Exacerbation:

Let's jump forward in time and say baby Matt is now 2 years and 6 month old. He presents to the CF clinic acutely unwell with increased cough and yellow sputum for the last 3 days. He has vomited once in the last 24 hours and has a decreased appetite. His temperature is 37.3 °C. His weight was 11.5kg last clinic visit 3 months ago, and today it is 10.4kg. His height is 87cm. On examination, bilateral crackles are heard with decreased air entry bilaterally. He had a positive culture for pan sensitive *Staphylococcus aureus* during a similar episode 6 months ago. During his infections with *S. aureus* 6 months ago he was treated with cefazolin 100 mg/kg per day in three or four divided doses for 14 days. His last throat culture from 3 months ago did not show any bacterial growths. What should we do with his today? First we should get an oropharyngeal swab to send for bacterial culture. We can also try to obtain a spontaneous or induced sputum culture, but as our child is only 2.5 years old it could be difficult to obtain. It is also important for us to start on treatment as soon as possible . Initial assessment reveals that he is stable, does not appear septic and does not warrant inpatient admission. Since we know he has grown *S. aureus* previously and had

done well on a course of cefazolin, we can initiate the same management. Our culture comes back as non-mucoid *Pseudomonas aeruginosa* co-infection with MSSA. In cases of co-infection we will need to change our treatment to **IV** ceftazidime **and** tobramycin. We want to eradicate the non-mucoid Pseudomonas as early infections can usually be cleared. We will follow up with repeat cultures in 2-3 weeks' times independent of symptoms. In case of Pseudomonas aeruginosa mucoid type, it often leads to chronic infection and is associated with a decline in lung function. Pseudomonas infection and colonization is often seen as a hallmark of CF. If surveillance cultures show reoccurrence of Pseudomonas, then long term antibiotics including a macrolide and inhaled tobramycin are recommended. To conclude it is so important to treat infections early and aggressively to decrease pulmonary exacerbations in children with CF. Acute exacerbations not only impairs their quality of life, but can lead to chronic infections and ultimately respiratory failure.

Review of Key Learning objectives:

In the second part of podcast we reviewed in detailed the complications of CF. The first being respiratory complications including: bacterial infections, allergic bronchopulmonary aspergillosis (ABPA), pneumothorax and nasal polyps. Then we discussed the GI complications of pancreatic insufficiency, DIOS, neonatal cholestasis and CF related diabetes. Finally, the complications of the reproductive system leading to infertility. We also looked at the diagnosis and management of an acute pulmonary exacerbation through a case analysis. It is important to remember to start antibiotics early and to continue until eradication. If the infection is chronic, long term antibiotic therapy may be needed. Pulmonary exacerbations are one of the leading causes of morbidity and mortality in children with CF.

To end this series of podcasts examining CF in the pediatric population, I also want to emphasize the impact of a chronic disease on the day to day lives of patients and their families. For most patients with CF, many hours are spent each day on maintanence therapy including multiple sets of chest physiotherapy, taking inhaled and oral medications, and managing various lifestyle and dietary therapies. This is not only socially and emotionally exhausting on the patients, but also their family members. It is important for us as health care providers to provide family centred care and consider and involve all members of the family in our treatment plan.

Test yourself :

1. What is the classic presentation of CF diagnosis in childhood?

Respiratory complications (productive cough, recurrent infections), and pancreatic insufficiency (steatorrhea, bulky pale and offensive stool) leading to persistent FTT.

2. What are some preventative infection control measures that are recommended for children with CF?

Infection control measures including good hygiene for example proper hand washing, room air ventilation, and cleaning surfaces as most bacterial and viral infections are spread through droplet and direct contact. It is recommended for children with CF to not interact with other children or adults who may be sick. In addition, children with CF cannot interaction with other children with CF especially in inpatient settings due to the risk of transmission of CF related pathogens.

3. What are the 3 most common causes of respiratory infection in children with CF?
Staphylococcus aureus, Haemophilus influenza and *Pseudomonas aeruginosa*

Thank you for listening and hope these podcasts have been helpful in furthering your knowledge of CF.

References

Ahmed MI, Mukherjee S. Treatment for chronic methicillin-sensitive Staphylococcus aureus pulmonary infection in people with cystic fibrosis. Cochrane Database Syst Rev. 2016;3:CD011581.

Amaral MD. Novel personalized therapies for cystic fibrosis: treating the basic defect in all patients. J Intern Med. 2015;277(2):155-66.

Boczar, M., Sawicka, E., & Zybert, K. (2015 jan-mar). Meconium ileus in newborns with cystic fibrosis - results of treatment in the group of patients operated on in the years 2000-2014. Developmental Period Medicine, 19(1), 32-40.

Burns, J., & Moss, R. (n.d.). Cystic Fibrosis Infection Control. *The Cystic Fibrosis Centre at Stanford*. Retrieved August 17, 2017, from https://med.stanford.edu/cfcenter/education/english/CFinfection-control.html.

Developed by Rose Sun, Dr. Tamizan Kherani and Dr. Melinda Solomon for PedsCases.com
October 7, 2021

Carlyle, B. E., Borowitz, D. S., & Glick, P. L. (2012). A review of pathophysiology and management of fetuses and neonates with meconium ileus for the pediatric surgeon. Journal of Pediatric Surgery,47(4), 772-781. doi:10.1016/j.jpedsurg.2012.02.019

Condren ME, Bradshaw MD. Ivacaftor: a novel gene-based therapeutic approach for cystic fibrosis. J Pediatr Pharmacol Ther. 2013;18(1):8-13.

Felix Ratjen, and Elizabeth Tullis. Airway Diseases: Section IX Cystic Fibrosis. Print. 593-601. Philadelphia: Elsevier Saunders.

Katharine D Wenstrom, . "Cystic Fibrosis: Carrier Screening." Louise Wilkins-Haug. Web UptoDate. 17 Apr. 2016.

Jessup, M., & Parkinson, C. (December 2, 2009). “All at Sea”: The Experience of Living With Cystic Fibrosis. *SAGE Journals*.

Margaret Lilley, Susan Christian, Stacey Hume, Patrick Scott, Mark Montgomery, Lisa Semple, Peter Zuberbuhler, Joan Tabak, Fiona Bamforth, and Martin Somerville. "Newborn Screening for Cystic Fibrosis in Alberta: Two Years of Experience." Paediatrics & Child Health (2010): 590-94. Web. 12 Apr. 2016.

Montgomery GS ,and Howenstine M. Cystic Fibrosis. Pediatrics in Review 2009; 30(8): 302-310.
Overview of Cystic Fibrosis.

Simon, R. H., Mallory, G. B., & Hoppin, A. G. (june 27, 2017). Cystic fibrosis: Antibiotic therapy for chronic pulmonary infection. *Uptodate*. Retrieved August 25, 2017, from https://www.uptodate.com/contents/cystic-fibrosis-antibiotic-therapy-for-chronic-pulmonary-infection#H25.

Tosco A, De gregorio F, Esposito S, et al. A novel treatment of cystic fibrosis acting on-target: cysteamine plus epigallocatechin gallate for the autophagy-dependent rescue of class II-mutated CFTR. Cell Death Differ. 2017;24(7):1305.

American Academy of Paediatric Section on Paediatric Pulmonology. Paediatric Pulmonology. Chapter 37: Cystic Fibrosis ed. Print. 718-743.

Centers for Disease Control and Prevention. Growth Charts, 2010. Web. 17 Apr. 2016. <http://www.cdc.gov/growthcharts/>.

Cystic Fibrosis Care Guidelines for Nutritional Management . Web. March 2018.

Developed by Rose Sun, Dr. Tamizan Kherani and Dr. Melinda Solomon for PedsCases.com
October 7, 2021

<https://www2.gov.bc.ca/assets/gov/health/practitioner-pro/bc-guidelines/cystic-fibrosis/cf_care_guidelines_for_nutrition_management.pdf>.

"Meconium Ileus." Merck Manuals Professional Edition. Web. 17 Apr. 2016. <https://www.merckmanuals.com/professional/pediatrics/perinatal-problems/meconium-ileus>.

"Neonatal Intestinal Obstruction." Neonatal Intestinal Obstruction. Web. 17 Apr. 2016. <https://pedclerk.bsd.uchicago.edu/page/neonatal-intestinal-obstruction>.

Developed by Rose Sun, Dr. Tamizan Kherani and Dr. Melinda Solomon for PedsCases.com
October 7, 2021