CYSTIC FIBROSIS LIVER DISEASE pdf

1: Researchers identify risk factors of advanced liver disease in cystic fibrosis patients

Introduction. Cystic fibrosis (CF) is the most common genetic disease occurring in Caucasians, of autosomal-recessive inheritance. It is a systemic disease, in the course of which pathologies of different systems and organs can be observed.

Overview What is cystic fibrosis liver disease? Cystic fibrosis liver disease CFLD only affects patients that have cystic fibrosis CF , a genetic disorder that primarily affects the lungs and the pancreas, but can also create problems in the liver and other organs. CF is caused by changes, called mutations, in the gene for the cystic fibrosis conductance transmembrane regulator CFTR , a protein that helps the body create normal mucus and clear it from the cells. Because the protein is abnormal, patients make too much mucus that is too thick to clear from the lining of their organs. The main problems in most patients with CF are in the lungs and pancreas. Mild liver problems are also common in CF. These include slightly elevated liver blood tests or fat in the liver. What causes cystic fibrosis liver disease? The exact cause of CFLD is not known. Most researchers suspect that the reduced function of the CFTR protein in the liver of patients with CF leads to thick bile that can plug the small bile ducts in the liver. These plugs may trigger the inflammation and scarring of the liver found in CFLD. Who gets cystic fibrosis liver disease? Signs and Symptoms What are the signs and symptoms of cystic fibrosis liver disease? CF patients with mild liver problems usually do not have any symptoms. In patients with advanced CFLD, an enlarged spleen or liver is the most common finding. As the advanced CFLD progresses, high pressure in the portal vein, the large vein that brings blood to the liver develops portal hypertension. This can lead to accumulation of fluid in the abdomen and bleeding from dilated veins called varices in the esophagus or stomach. In some patients, poor nutrition can also develop as a result of CFLD. Tests and Diagnosis What tests are used to diagnose cystic fibrosis liver disease? An abdominal ultrasound, CT scan or MRI are the main imaging tests used to make the diagnosis because they allow doctors to examine the liver for signs of scarring. A liver biopsy can also be helpful in diagnosing CFLD. During a biopsy, a small sample of the liver is taken from a patient and examined under a microscope. CFLD is usually suspected after a doctor finds an enlarged spleen or liver during an exam. The next step is usually blood tests to look for other potential causes of liver disease and an abdominal ultrasound to look for scarring in the liver. Treatment How is cystic fibrosis liver disease treated? At the Pediatric Liver Center, doctors, nurses, social workers and dietitians with experience treating patients with CF and CFLD design the best treatment approach for each patient. Although there is no known cure for CFLD, there are ways to reduce the effects of the disease. Usually, a combination of attention to diet and use of medications and procedures, such as endoscopy, are combined. Most children with CFLD can lead long, productive lives managing their condition. We have vast experience with CFLD and are at the forefront of research and testing for new medicines. We provide early access to clinical trials of new treatments for CFLD.

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2: Liver disease in cystic fibrosis

Cystic fibrosis (CF) is a genetic condition affecting the lungs, liver, intestines, pancreas and reproductive organs. In the lungs, thick mucus has difficulty getting out of the lungs causing chronic lung disease.

Open in a separate window In infants with cystic fibrosis, liver dysfunction may occur in the form of cholestasis. In the pathomechanism of this phenomenon, the thickening processes of acidophilic secretion in the intrahepatic bile ducts are taken into consideration. In laboratory tests, an increased concentration of conjugated bilirubin clinically accompanied by discoloured stools may be observed, which may incorrectly suggest a diagnosis of atresia of the extrahepatic bile ducts. The symptoms usually relieve spontaneously; however, in some patients liver fibrosis may develop [2]. In patients with cystic fibrosis, other irregularities within bile ducts are also observed, such as cholelithiasis and cholecystitis, the incidence of which increases with age. There is often a reduction in the gallbladder dimension, which, together with increased bile viscosity, promotes the development of cholelithiasis. The small gallbladder is mostly asymptomatic and is only incidentally detected in ultrasound tests. In some adult patients with cystic fibrosis, symptoms similar to those of primary sclerosing cholangitis PSC occur. In some patients, common bile duct obstruction may also occur, manifesting as abdominal pain and jaundice [2]. Bleeding from the upper part of the digestive tract rarely occurs as a first symptom of CFLD, which is connected with a focus on early identification of CFLD risk factors, particularly portal hypertension [2]. In older children and adults, CFLD includes three stages of advanced pathological lesions: The causes of hepatic steatosis secondary to cystic fibrosis have yet to be fully explored. Pathogenesis is not directly connected with a defective CFTR gene, but it may be related to malnutrition, deficiencies of essential fatty acids, carnitine or choline, oxidative stress as well as insulin resistance, commonly occurring in patients with cystic fibrosis [3]. It is not fully clear whether hepatic steatosis is progressive and inevitably leads to liver cirrhosis, or whether this process is reversible. Clinically, hepatic steatosis manifests as liver enlargement, and ultrasound examination exposes the hyperechogenic structure of the liver tissue. It is worth emphasising that normal size of the liver and correct transaminase activity is not unequivocal in excluding hepatic steatosis. The treatment of hepatic steatosis should be aimed at improving the nutritional status of the patient, including supplementation with fat-soluble vitamins, particularly in patients with associated cholestasis. Due to the fact that hepatic steatosis can be asymptomatic during the initial stage, ultrasound examination of the abdominal cavity should be performed at least once a year in all patients with cystic fibrosis, as well as a basic biochemical evaluation of liver function. Cirrhosis is a final, irreversible stage of liver damage that leads to the failure of the organ. The clinical presentation of advanced liver cirrhosis includes jaundice, coagulation process disorders, ascites and the development of portal hypertension. Children with cystic fibrosis develop portal hypertension and oesophageal varices in the course of cirrhosis, linked to a risk of haemorrhage that may cause an immediate and vital risk. Portal hypertension is accompanied by splenomegaly with a decreased number of thrombocytes and leukocytes. The activity of hepatocytes is maintained, symptoms of liver failure are not observed and in laboratory tests, except for the above-mentioned haematological irregularities thrombocytopaenia, leukopaenia , aberrations are often not observed. Biochemical exponents of liver failure increased level of bilirubin, decreased concentration of albumins and extension of prothrombin time appear late in advanced liver failure. Ultrasonography is a primary test carried out in patients with suspected cirrhosis of the liver. Early diagnosis of CFLD is very important because clinical symptoms appear late, when hepatobiliary system damage is already very advanced. Some studies suggest that only during the early stages are histopathological changes reversible and may be efficaciously treated. In everyday clinical practice, four tools for identification of CFLD are commonly used: In some centres, to assess the advancement of the disease, an endoscopic test of upper gastrointestinal tract oesophagus varices and stomach evaluation is performed, as well as a histological test of liver bioptates [2 , 13]. For these criteria, CFLD diagnosis should be based on a positive result from the CFLD histological test characteristics of focal and multilobular biliary cirrhosis or should meet at least two of the following criteria, evaluated at least twice a year: Comprehensive clinical evaluation of a patient with cystic fibrosis,

observed for CFLD, should be focused on the occurrence of the following symptoms: The physical examination should include: Biochemical tests are also used to establish the diagnosis of CFLD. It is believed that hypertransaminasaemia is not a sufficiently sensitive and specific exponent of CFLD, as it can show mild severity or occur temporarily, and correlates poorly with the degree of severity of liver damage. Other, less frequently used biochemical tests used in the evaluation of CFLD are: Among the imaging tests in patients with clinical symptoms or laboratory exponents of CFLD, ultrasonography plays an important role in the diagnostic process. This test allows the evaluation of focal biliary fibrosis, multilobular cirrhosis, hepatic steatosis, biliary duct abnormalities and abnormalities of blood flow in the portal vein Doppler US. In some patients, a liver biopsy is helpful in the diagnosis of CFLD. The CFLD pathognomonic lesions in the hepatic tissue are focal biliary cirrhosis. A liver biopsy allows one to differentiate between focal biliary cirrhosis and hepatic steatosis; it allows the assessment of the extension of fibrosis processes and allows the exclusion of other causes of liver dysfunction. Contraindications to performing this procedure are thrombocytopaenia and ascites in these situations either a laparoscopic approach or via the cervical vein may be considered [2]. Other imaging tests used in the diagnosis and assessment of CFLD advancement include: Currently it is believed that CFLD should be treated as an early complication of cystic fibrosis. For this reason, all patients with cystic fibrosis should be observed carefully for the occurrence of this complication in the first decade of life. This is especially applicable for patients with a high risk of CFLD development, i. Table II provides a list of laboratory tests for CFLD occurrence, which should be performed annually in patients with cystic fibrosis. In terms of the symptoms and complications of the respiratory system, the diagnosis of CFLD does not significantly change the clinical course of the disease. However, in some patients a rapid clinical deterioration may occur. The nutritional status of the patient should be also assessed systematically [8].

CYSTIC FIBROSIS LIVER DISEASE pdf

3: Cystic Fibrosis | National Heart, Lung, and Blood Institute (NHLBI)

Cystic fibrosis liver disease is the third most frequent cause of death in CF after respiratory and transplantation complications and accounts for % of all mortality. Liver disease is the initial diagnostic finding in % of patients, suggesting that all patients with unexplained cirrhosis should have a sweat test as part of their.

This causes thick, sticky mucus and very salty sweat. Research suggests that the CFTR protein also affects the body in other ways. This may help explain other symptoms and complications of CF. More than a thousand known defects can affect the CFTR gene. The type of defect you or your child has may affect the severity of CF. Other genes also may play a role in the severity of the disease. How Is Cystic Fibrosis Inherited? Every person inherits two CFTR genesâ€"one from each parent. However, they can pass the faulty CFTR gene to their children. A person inherits two copies of the CFTR geneâ€"one from each parent. If each parent has a normal CFTR gene and a faulty CFTR gene, each child has a 25 percent chance of inheriting two normal genes; a 50 percent chance of inheriting one normal gene and one faulty gene; and a 25 percent chance of inheriting two faulty genes. Risk Factors Cystic fibrosis CF affects both males and females and people from all racial and ethnic groups. However, the disease is most common among Caucasians of Northern European descent. The disease is less common among African Americans and Asian Americans. More than 10 million Americans are carriers of a faulty CF gene. Signs, Symptoms, and Complications The signs and symptoms of cystic fibrosis CF vary from person to person and over time. Other times, your symptoms may become more severe. Most of the other signs and symptoms of CF happen later. Cystic Fibrosis Figure A shows the organs that cystic fibrosis can affect. Figure B shows a cross-section of a normal airway. Figure C shows an airway with cystic fibrosis. The widened airway is blocked by thick, sticky mucus that contains blood and bacteria. This buildup of mucus makes it easier for bacteria to grow and cause infections. An infection caused by these bacteria may be a sign of CF. People who have CF have frequent bouts of sinusitis si-nu-SI-tis , an infection of the sinuses. The sinuses are hollow air spaces around the eyes, nose, and forehead. Frequent bouts of bronchitis bron-KI-tis and pneumonia nu-MO-ne-ah also can occur. These infections can cause long-term lung damage. Some people who have CF also develop nasal polyps growths in the nose that may require surgery. Digestive System Signs and Symptoms In CF, mucus can block tubes, or ducts, in your pancreas an organ in your abdomen. These blockages prevent enzymes from reaching your intestines. This can cause ongoing diarrhea or bulky, foul-smelling, greasy stools. Intestinal blockages also may occur, especially in newborns. Too much gas or severe constipation in the intestines may cause stomach pain and discomfort. A hallmark of CF in children is poor weight gain and growth. These children are unable to get enough nutrients from their food because of the lack of enzymes to help absorb fats and proteins. As CF gets worse, other problems may occur, such as: This is a condition in which the pancreas become inflamed, which causes pain. Frequent coughing or problems passing stools may cause rectal tissue from inside you to move out of your rectum. Liver disease due to inflamed or blocked bile ducts. The vas deferens is a tube that delivers sperm from the testes to the penis. Women who have CF may have a hard time getting pregnant because of mucus blocking the cervix or other CF complications. Other Signs, Symptoms, and Complications Other signs and symptoms of CF are related to an upset of the balance of minerals in your blood. CF causes your sweat to become very salty. As a result, your body loses large amounts of salt when you sweat. This can cause dehydration a lack of fluid in your body , increased heart rate, fatigue tiredness , weakness, decreased blood pressure, heat stroke, and, rarely, death. CF also can cause clubbing and low bone density. Clubbing is the widening and rounding of the tips of your fingers and toes. Low bone density also tends to occur late in CF. It can lead to bone-thinning disorders called osteoporosis and osteopenia. Diagnosis Doctors diagnose cystic fibrosis CF based on the results from various tests. The genetic test shows whether a newborn has faulty CFTR genes. Sweat Test If a genetic test or blood test suggests CF, a doctor will confirm the diagnosis using a sweat test. This test is the most useful test for diagnosing CF. A sweat test measures the amount of salt in sweat. For this test, the doctor triggers sweating on a small patch of skin on an arm or leg. He or she rubs the skin with a sweat-producing chemical and then uses an electrode to provide a mild electrical current. This may cause a tingling or warm

feeling. Sweat is collected on a pad or paper and then analyzed. The sweat test usually is done twice. High salt levels confirm a diagnosis of CF. Other Tests If you or your child has CF, your doctor may recommend other tests, such as: A chest x ray. This test creates pictures of the structures in your chest, such as your heart, lungs, and blood vessels. A chest x ray can show whether your lungs are inflamed or scarred, or whether they trap air. A sinus x ray. This test may show signs of sinusitis, a complication of CF. These tests measure how much air you can breathe in and out, how fast you can breathe air out, and how well your lungs deliver oxygen to your blood. For this test, your doctor will take a sample of your sputum spit to see whether bacteria are growing in it. If you have bacteria called mucoid Pseudomonas, you may have more advanced CF that needs aggressive treatment. In amniocentesis, your doctor inserts a hollow needle through your abdominal wall into your uterus. He or she removes a small amount of fluid from the sac around the baby. In CVS, your doctor threads a thin tube through the vagina and cervix to the placenta. The doctor removes a tissue sample from the placenta using gentle suction. The sample is tested to see whether the baby has CF. CF carriers usually have no symptoms of CF and live normal lives. However, carriers can pass faulty CFTR genes on to their children. A genetics counselor can test a blood or saliva sample to find out whether you have a faulty CF gene. This type of testing can detect faulty CF genes in 9 out of 10 cases. Treatment Cystic fibrosis CF has no cure. However, treatments have greatly improved in recent years. The goals of CF treatment include: Preventing and controlling lung infections Loosening and removing thick, sticky mucus from the lungs Preventing or treating blockages in the intestines Providing enough nutrition Preventing dehydration a lack of fluid in the body Depending on the severity of CF, you or your child may be treated in a hospital. This is a doctor who is familiar with the complex nature of CF. Often, a CF specialist works with a medical team of nurses, physical therapists, dietitians, and social workers. CF specialists often are located at major medical centers. These centers have teams of doctors, nurses, dietitians, respiratory therapists, physical therapists, and social workers who have special training related to CF care. Most CF Care Centers have pediatric and adult programs or clinics. Your doctor also may recommend a pulmonary rehabilitation PR program. It involves pounding your chest and back over and over with your hands or a device to loosen the mucus from your lungs so that you can cough it up. You might sit down or lie on your stomach with your head down while you do CPT. Gravity and force help drain the mucus from your lungs. Some people find CPT hard or uncomfortable to do. Several devices have been developed that may help with CPT, such as: An electric chest clapper, known as a mechanical percussor. A small, handheld device that you exhale through. The device causes vibrations that dislodge the mucus. A mask that creates vibrations that help break the mucus loose from your airway walls. Breathing techniques also may help dislodge mucus so you can cough it up.

CYSTIC FIBROSIS LIVER DISEASE pdf

4: Cystic fibrosis - Wikipedia

Advanced liver disease is a complication that affects about seven percent of all individuals with cystic fibrosis and is the third leading cause of death in cystic fibrosis.

This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited. This article has been cited by other articles in PMC. Abstract Context Cystic fibrosis CF is the most widespread autosomal recessive genetic disorder that limits life expectation amongst the Caucasian population. As the median survival has increased related to early multidisciplinary intervention, other manifestations of CF have emergedespecially for the broad spectrum of hepatobiliary involvement. The present study reviews the existing literature on liver disease in cystic fibrosis and describes the key issues for an adequate clinical evaluation and management of patients, with a focus on the pathogenetic, clinical and diagnostic-therapeutic aspects of liver disease in CF. Evidence Acquisition A literature search of electronic databases was undertaken for relevant studies published from about liver disease in cystic fibrosis. The databases searched were: Results CF is due to mutations in the gene on chromosome 7 that encodes an amino acidic polypeptide named CFTR cystic fibrosis transmembrane regulator. The hepatic manifestations include particular changes referring to the basic CFTR defect, iatrogenic lesions or consequences of the multisystem disease. Conclusions Liver disease will have a growing impact on survival and quality of life of cystic fibrosis patients because a longer life expectancy and for this it is important its early recognition and a correct clinical management aimed atdelaying the onset of complications. This review could represent an opportunity to encourage researchers to better investigate genotype-phenotype correlation associated with the development of cystic fibrosis liver disease, especially for non-CFTR genetic polymorphisms, and detect predisposed individuals. Therapeutic trials are needed to find strategies of fibrosis prevention and to avoid its progression prior to development its related complications. Cystic Fibrosis, Liver Disease, Mutation 1. Context Cystic fibrosis CF is the most widespread autosomal recessive genetic disorder that limits life expectation amongst the Caucasian population. The approximate occurrence of CF is 1 in newborns 1. There is a great heterogeneity in clinical manifestations and the disease affects many organs but the most notable arelungs, reproductive tracts, pancreas,intestine and liver 2. CF is due to mutations in the gene on chromosome 7 that encodes an amino acidic polypeptide named CFTR cystic fibrosis transmembrane regulator. CFTR is a protein acting as an anion channel and it is expressed on epithelial cells throughout the body 3. The most frequent mutation is p. CFTR mutations can be divided into 6 different classes according to their predicted functional consequences for the CFTR protein 6 , 7. Class I mutations alter the biosynthesis and results in the total or partial absence of the protein. Class II mutations, including p. Phedel, lead to defective protein maturation and processing. Class III mutations disturb the regulation of chloride channel, leading to the formation of non-functional CFTR protein at the apical membrane. Class IV mutationslead to altered channel conductance. Class V mutations affect the stability of mRNA. In general, class I, II, III and VI mutations are associated with pancreatic insufficiency, higher frequency of meconium ileus, premature mortality and are thus considered severe mutations. Class IV-V is usually associated with a mild disease. CF is no longer considered an exclusively pediatric disease as nowadays life expectation is over 35 years. The hepatic manifestations include particular changes referring to thebasic CFTR defect, iatrogenic lesions or consequences of the multisystem disease 2. Cirrhosis occurred in 19 7. Liver failure is a late occurrence in CF patients, especially after the pediatric age and occasionally before it This highlights that the pathogenetic mechanism is produced by several factors. In addition to severe genotype, other risk factors of CFLD might include male gender, pancreatic insufficiency, severity of pulmonary disease and neonatal meconium ileus 14 - They also reported that the early recognition of CF is very important because the delayed diagnosis facilitated the development of CFLD The present study reviews the existing literature on liver disease in cystic fibrosis and describes the key issues for an adequate clinical evaluation and management of patients with a focus on the pathogenetic, clinical and diagnostic-therapeutic aspects of CFLD. CFTR in biliary epithelium increases apical biliary

chloride secretion primarily increasing bile acid independent bile flow The abnormal activity or the absence of CFTR could decrease bile fluidity and alkalinity, causing accumulation and precipitation of hyperviscous biliary secretions in intrahepatic tree Inspissated bile accumulates in the biliary ducts leading to cholangiocyte and hepatocyte injury, stimulating focal fibrosis This has been hypothesized to lead to the accumulation of toxic bile acids in the liver, depletion of hepatic antioxidants, and liver cell injury. Another theory of pathogenesis is that increased intestinal permeability in CF leads to absorption of pathogen associated molecular patterns that stimulate inflammation and fibrosis 24 - It is unknown why only a subset of CF patients develops cirrhosis, while the majority of individuals with a similar CFTR defect do not develop cirrhosis [19]. In this regard, Wilshanski et al. These authors found a prevalence of liver disease increased with age but no correlation was found between liver disease and a history of meconium ileus, nutritional status or severity of lung disease One sibling of each of the five sets was free of liver involvement, and the other had a severe liver expression, demonstrating that nutritional state, environmental factors, and therapy compliance are not involved in the liver expression of CF and modifier genes, inherited independently of the CFTR gene, might be important in the development of CFLD In , Pereira et al. The authors demonstrated a different expression of several genes associated with hepatic fibrogenesis including, matrix metalloproteinases, collagens and chemokines in CFLD versus the control patients, particularly decreased expression in tissue remodelling genes including tissue inhibitor of metalloproteinase-1 TIMP-1 and plasminogen activator inhibitor-1 PAI-1, up to fold These studies show a possible genetic predisposition, independent of the CFTR gene, in the pathogenesis of CFLD but further data are needed to add details about this issue. Clinical Presentation The wide spectrum of manifestations includes neonatal cholestasis, isolated elevated values of transaminases, hepatic steatosis, hepatic fibrosis, focal or multilobular cirrhosis with or without portal hypertension. The routine physical examination often shows an enlarged liver, even if the liver function tests could result normal 2 , 12 , On clinical examination, the infants affected by neonatal cholestasis could appear with jaundice, which is observed also in patients with end-stage multilobular biliary cirrhosis The underlyingCF secretory defect at the hepatobiliary level seems to not directly influence the pathogenesis of steatosis. It has not been demonstrated that steatosis progresses to cirrhosis and it is accepted considered as a relatively benign condition in CF. However, it is known that nonalcoholic steatohepatitis may cause cirrhosis in adults 36 , therefore further studies are needed to add new data on this issue. Due to the extension of the fibrogenic cascade, focal biliary cirrhosis evolves into multilobular cirrhosis and its related complications such as splenomegaly with hypersplenism, esophageal or gastric varices, ascites and encephalopathy Multilobular cirrhosis differs from focal biliary cirrhosis for the presence of multiple regenerative nodules and diffuses involvement of the liver. Clinically multilobular cirrhosis is detected by a hard nodular liver that may or may not be enlarged. Prior to the development of portal hypertension, there are often no other clinical features. Once portal hypertension is present, splenomegaly, upper gastrointestinal bleeding secondary to esophageal or gastric varices, or ascites may be the first suggestion of previously unsuspected cirrhosis There is also another fatty infiltration pattern that is called pseudomasses. These typical structures can be described as hyperechoic areas cm in diameter, which can be visualized as heterogenic liver parenchyma using imaging techniques 38 , These stones are more commonly calcium bilirubinate stones Morphological assessment could document abnormal cholangiographic findings referring to sclerosing cholangitis in children and adult patients with CFLD. The fibrogenic process stimulates an inflammatory cascade that involves biliary tract and causes proteinprecipitation and bile ducts compression, causing sclerosis cholangitis 38 , Few case reports documented the occurence of hepatocellular carcinoma HCC in these patients. Table 1 summarizes the hepatobiliary clinical findings in CF. The evolution of CFLD is usually slow and progressive:

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5: Cystic Fibrosis Liver Disease | Children's Hospital Colorado

Cystic fibrosis (CF) patients with liver disease do not experience greater lung function decline compared with CF patients without liver presentation, a study reports. The study, "Analysis of a large cohort of cystic fibrosis patients with severe liver disease indicates lung function decline does.

Cystic fibrosis liver disease is the third most frequent cause of death in CF after respiratory and transplantation complications and accounts for 2. Liver disease is the initial diagnostic finding in 1. The only potentially curative treatment for liver failure the development of jaundice, ascites and encephalopathy is transplantation. However, even in established cases of cirrhosis, serum liver enzymes may be completely normal. Early detection of liver disease is thus of vital importance to allow treatment to prevent or delay its progression. Due to the increased and widespread use of laboratory tests, and clinical and ultrasound examination, more patients with CF are now diagnosed with only minor degrees of liver involvement. Anatomy of the liver, spleen, gall bladder and pancreas Pathogenesis and aetiology Cystic fibrosis liver disease is due to impaired secretory function of the biliary epithelium and therefore absent or dysfunctional CFTR protein is fundamental to its pathogenesis Colombo et al, The CFTR protein is expressed exclusively at the apical domain of epithelial cells lining the intra- and extrahepatic bile ducts and gall bladder Cohn et al, ; Kinnman et al, It is not expressed in hepatocytes or other cells of the liver and its main role is to participate in the first stage of ductal secretion. It is thought that the primary chloride channel defect results in dehydrated, inspissated secretions that plug and obstruct the intrahepatic bile ducts and initiate a progressive periportal fibrosis. This theory, however, fails to explain why only a third of patients develop clinically significant liver disease and why CFLD shows such variable severity despite all patients having absent or abnormal CFTR function. This variability might be explained by non-CFTR modifying genetic or environmental factors that determine whether or not liver changes will progress to clinical significance in any given case. There has been much research in this area. The existence of modifier genes has been suggested by sibling studies Castaldo et al, It seems likely that multiple genes are involved. Those under current study include alphaantitrypsin, transforming growth factor, and mannose binding lectin Lewindon et al, ; Salvatore et al, The presence of mutations or variants in all three genes has been associated with the greatest risk of developing CFLD with an odds ratio of Cystic fibrosis transmembrane conductance regulator modulates glutathione transport and thus CFTR dysfunction creates an imbalance in antioxidant defences. The glutathione genotype is expressed in the biliary epithelium in significantly higher amounts in patients with CF liver disease. Amongst the youngest patients with CF this genotype has been associated with an eight fold increase in the risk of liver disease. Identification of this and other polymorphisms may have prognostic value and prompt early treatment in patients at increased risk of liver disease. Other factors, intrinsic to the patient may determine whether CFLD will develop. Several studies cite a higher risk in male patients, in those with a history of meconium ileus 5-fold increase and in those with a severe CFTR mutation Colombo et al, ; Colombo et al, ; Lamireau et al, Although not universal Slieker et al, , meconium ileus has been recognised as a risk factor in most studies. Possible explanations include prolonged bowel obstruction which may influence biliary secretion and cause plugging in the biliary tree, extensive surgical management and total parenteral nutrition Shapira et al, This suggests a possible protective role of UDCA against liver injury. They also reported that children with established CFLD had evidence of impaired growth and nutrition and worse pulmonary status Corbett et al, Several other studies have not found this association Colombo et al, ; Slieker et al, ; Lamireau et al, The available data seem to indicate that nutritional status is not a causal factor of CFLD, but that patients with CFLD are at increased risk for deterioration of nutritional status Corbett et al, ; Colombo et al, A combination of factors causes secondary hepatocyte injury. Bile acid malabsorption results in retention of hepatotoxic glycine conjugated bile acids. Focal biliary cirrhosis is the most clinically relevant hepatic problem associated with CF, since extension of the focal process may lead to multilobular biliary cirrhosis and the development of portal hypertension Sokol et al, This process may take years or even decades during which there may be no clinical or biochemical manifestations of deteriorating liver health. As in other conditions characterised by

initial involvement of bile ducts and later impairment of hepatocyte function, liver failure tends to be a late event Colombo et al, Incidence and prevalence The true incidence of CFLD is difficult to determine as there are no sensitive or specific diagnostic markers. Earlier studies reported a peak incidence in adolescence, decreasing by the third decade of life Scott-Jupp et al, In the latter study no patient developed clinical liver disease in adulthood. During a 14 year median follow-up in a prospective assessment the incidence rate number of new cases per year of CFLD was 1. The mean age at diagnosis was 7. In another prospective study the incidence of cirrhosis was 4. Prevalence total number of cases data for CFLD are similarly bedevilled by a lack of specific diagnostic markers and the different criteria used for patient selection in different studies. The last decade has been characterised by the active search for CFLD and increased recognition of asymptomatic patients with focal biliary cirrhosis Colombo et al, In the same study, the presence of CFLD was not associated with more severe pulmonary disease. The reported prevalence of portal hypertension varies from 1. Liver disease is thus a frequent and early complication of CF. Attempts at diagnosis should focus on the first decade of life. Clinical presentation Cystic fibrosis liver disease is often difficult to define clinically as it initially causes no symptoms and shows inconsistent abnormalities in serum liver function tests. Often abnormalities will only be seen on histology or ultrasound examination. The most common clinical presentation is an enlarged liver on routine physical examination, with or without associated abnormalities in liver biochemistry. Jaundice is generally limited to babies with neonatal cholestasis or to those with end-stage multilobular biliary cirrhosis. Early detection can be difficult, but should be actively pursued because only early lesions are likely to be reversible. Patients may present with complications of CFLD, the most severe of which is portal hypertension, suggested by splenomegaly, hypersplenism and upper gastrointestinal bleeding secondary to oesophageal or gastric varices Colombo et al, As focal biliary cirrhosis progresses to multilobular cirrhosis the complications of portal hypertension appear at an unpredictable pace. As in other liver diseases characterised by initial involvement of the bile ducts, liver failure is a late event Tanner et al, Once multilobular cirrhosis and portal hypertension are established the prognosis is poor. Its pathogenesis has not been definitely established, but it does not seem directly related to the CF secretory defect Fields et al, Massive steatosis was once frequently observed in newly diagnosed patients with pancreatic insufficiency and severe malnutrition, but has now become less frequent due to earlier diagnosis and appropriate nutritional care. In less severe forms, it has been associated with nutritional deficiencies e. There is no evidence to suggest that steatosis progresses to cirrhosis and it is recognised as a relatively benign condition. Screening for liver disease Patients should be examined routinely for hepatosplenomegaly large liver and spleen at every visit. Upper abdominal ultrasound examination and serum liver function tests should be part of the annual assessment. Liver function tests Liver function test results may be intermittently elevated and do not always correlate with the severity of hepatic lesions. Transient elevation of liver function tests may be seen with hypoxaemia, antibiotic treatment and during a pulmonary exacerbation. Thus serial measurements should be performed. Liver enzymes originating from the biliary epithelium gamma-GT, 5-nucleotidase and the biliary isoenzyme of alkaline phosphatase are more specific for CFLD. Biochemical and ultrasonographic assessment may reflect different aspects of disease progression Williams et al, A combination of several tests is needed to reliably detect liver disease. The United States CF Foundation recommends that significant liver disease should be suspected if any liver enzyme is more than 1. Abdominal ultrasound Upper abdominal ultrasound is the investigation of choice to look for hepatobiliary problems and for long term follow up Williams et al, ; Stewart, As a screening tool it has advantages over other investigations. The relative paucity of body fat in children makes them good subjects. There is no ionising radiation. The procedure is usually well tolerated. Structures down to one millimetre size can be seen in detail and with very high resolution Stewart, Liver size and texture, steatosis, the presence of associated splenomegaly and gallbladder abnormalities can be assessed. Several studies have looked for a correlation between ultrasound findings and biochemical test results. The ultrasound scan may thus select a subgroup of patients who have focal hepatic lesions with normal hepatic function. These patients are more likely to respond to early intervention therapy with ursodeoxycholic acid UDCA. For a better evaluation of portal hypertension, ultrasound can be used in association with Doppler studies of the portal vein, which can detect dilatation and flow patterns of the hepatic vasculature Vergesslich

et al, Portal hypertension is suggested by decreased portal venous flow velocities or reversal of flow hepatofugal in the portal vein. Scintigraphy Hepatobiliary scintigraphy with the technetium labelled isotope DISIDA represents another non-invasive means of assessing both liver function and biliary excretion. The most common abnormality seen is beading of the intrahepatic ducts, followed by retention of activity within the liver, increased visualisation of secondary ducts and non-visualisation of the gallbladder. Results from this study showed that a combination of investigations is required for reliable follow-up of liver disease. This is probably because different parameters of liver status are measured by the different tests. Delayed intestinal visualisation at hepatobiliary scintigraphy is associated with a better response to long term treatment with UDCA Colombo et al, Computed tomography and magnetic resonance imaging Several studies have described magnetic resonance MR and computed tomography CT findings in patients with cystic fibrosis King et al, ; Akata et al, Magnetic resonance cholangiography MRC is a non-invasive procedure that provides a high quality picture of any abnormalities of the intra- and extra-hepatic bile ducts King et al, Repeat MR examinations can be performed to evaluate disease progression or response to therapy without any radiation exposure, or the difficulties encountered by comparison of findings in serial ultrasound examinations performed by different observers Akata et al, Liver biopsy The role of percutaneous liver biopsy is controversial. It is an invasive procedure and early changes of liver disease are focal in nature and may therefore be missed by blind biopsy. Even though significant liver disease can be detected by biopsy in the presence of normal clinical and ultrasound examinations and normal liver enzyme levels Davidson et al, , a normal biopsy cannot exclude even advanced liver disease Lindblad et al, Nevertheless, liver biopsy may provide important information on the type of the predominant lesion steatosis or focal biliary cirrhosis , the extent of portal fibrosis, rate of progression and response to treatment. It should be performed if there is doubt about the diagnosis and to establish cirrhosis prior to treatment or transplantation Colombo et al, Treatment of liver disease Medical treatment Therapy is aimed at improving biliary excretion and bile acid composition. UDCA is a naturally occurring hydrophilic bile acid which improves biochemical indices of liver function Colombo et al, ; Sokol et al, Ursodeoxycholic acid augments bile flow, displaces toxic hydrophobic bile acids, stimulates bicarbonate secretion into bile and has a general cytoprotective cholangiocyte effect Kowdley, ; Gores, A 10 year prospective study of the effect of UDCA showed promising results in its ability to arrest the progression of early focal lesions Nousia-Arvanitakis et al, Seventy individuals with ultrasound evidence of multifocal liver disease were commenced on UDCA. After 10 years the progression of nodular biliary cirrhosis, shown by ultrasound examination, was arrested, hepatic function preserved and no variceal bleeding observed.

CYSTIC FIBROSIS LIVER DISEASE pdf

6: Cystic fibrosis and liver disease

Advanced liver disease is a complication that affects about seven percent of all individuals with cystic fibrosis and is the third leading cause of death in cystic fibrosis. Primarily, this is a.

In the early stages, incessant coughing, copious phlegm production, and decreased ability to exercise are common. Many of these symptoms occur when bacteria that normally inhabit the thick mucus grow out of control and cause pneumonia. In later stages, changes in the architecture of the lung, such as pathology in the major airways bronchiectasis , further exacerbate difficulties in breathing. Other signs include coughing up blood hemoptysis , high blood pressure in the lung pulmonary hypertension , heart failure , difficulties getting enough oxygen to the body hypoxia , and respiratory failure requiring support with breathing masks, such as bilevel positive airway pressure machines or ventilators. Another is infection with Mycobacterium avium complex, a group of bacteria related to tuberculosis , which can cause lung damage and does not respond to common antibiotics. This may cause facial pain, fever, nasal drainage, and headaches. Individuals with CF may develop overgrowth of the nasal tissue nasal polyps due to inflammation from chronic sinus infections. Meconium may completely block the intestines and cause serious illness. These secretions block the exocrine movement of the digestive enzymes into the duodenum and result in irreversible damage to the pancreas, often with painful inflammation pancreatitis. Malabsorption leads to malnutrition and poor growth and development because of calorie loss. Resultant hypoproteinemia may be severe enough to cause generalized edema. Bile secreted by the liver to aid in digestion may block the bile ducts , leading to liver damage. Over time, this can lead to scarring and nodularity cirrhosis. The liver fails to rid the blood of toxins and does not make important proteins, such as those responsible for blood clotting. Damage of the pancreas can lead to loss of the islet cells, leading to a type of diabetes unique to those with the disease. Poor uptake of vitamin D from the diet because of malabsorption can lead to the bone disease osteoporosis in which weakened bones are more susceptible to fractures. In severe cases, malnutrition disrupts ovulation and causes a lack of menstruation. Thus, CF is considered an autosomal recessive disease. The CFTR gene, found at the q More specifically, the location is between base pair ,, and ,, on the long arm of chromosome 7, region 3, band 1, subband 2, represented as 7q The product of this gene the CFTR protein is a chloride ion channel important in creating sweat, digestive juices, and mucus. It also contains two domains comprising six alpha helices apiece, which allow the protein to cross the cell membrane. A regulatory binding site on the protein allows activation by phosphorylation , mainly by cAMP-dependent protein kinase. One example is mannan-binding lectin , which is involved in innate immunity by facilitating phagocytosis of microorganisms. Polymorphisms in one or both mannan-binding lectin alleles that result in lower circulating levels of the protein are associated with a threefold higher risk of end-stage lung disease, as well as an increased burden of chronic bacterial infections. When the CFTR protein is working correctly, ions freely flow in and out of the cells. However, when the CFTR protein is malfunctioning, these ions cannot flow out of the cell due to a blocked channel. This causes cystic fibrosis, characterized by the buildup of thick mucus in the lungs. Several mutations in the CFTR gene can occur, and different mutations cause different defects in the CFTR protein, sometimes causing a milder or more severe disease. These protein defects are also targets for drugs which can sometimes restore their function. Other mutations result in proteins that are too short truncated because production is ended prematurely. Other mutations produce proteins that do not use energy in the form of ATP normally, do not allow chloride, iodide, and thiocyanate to cross the membrane appropriately, [46] and degrade at a faster rate than normal. Mutations may also lead to fewer copies of the CFTR protein being produced. The protein spans this membrane and acts as a channel connecting the inner part of the cell cytoplasm to the surrounding fluid. This channel is primarily responsible for controlling the movement of halogens from inside to outside of the cell; however, in the sweat ducts, it facilitates the movement of chloride from the sweat duct into the cytoplasm. When the CFTR protein does not resorb ions in sweat ducts, chloride and thiocyanate [47] released from sweat glands are trapped inside the ducts and pumped to the skin. Additionally hypothiocyanite , OSCN, cannot be produced by the immune defense system. Sodium is the most common cation in the extracellular

space. The excess chloride within sweat ducts prevents sodium resorption by epithelial sodium channels and the combination of sodium and chloride creates the salt, which is lost in high amounts in the sweat of individuals with CF. This lost salt forms the basis for the sweat test. These blockages lead to remodeling and infection in the lung, damage by accumulated digestive enzymes in the pancreas, blockage of the intestines by thick feces, etc. Several theories have been posited on how the defects in the protein and cellular function cause the clinical effects. The most current theory suggests that defective ion transport leads to dehydration in the airway epithelia, thickening mucus. The flow of ions from the cell and into this layer is determined by ion channels such as CFTR. CFTR not only allows chloride ions to be drawn from the cell and into the ASL, but it also regulates another channel called ENac, which allows sodium ions to leave the ASL and enter the respiratory epithelium. As water follows sodium, the depth of ASL will be depleted and the cilia will be left in the mucous layer. The presence of the same CFTR proteins in the pancreatic duct and sweat glands in the skin also cause symptoms in these systems. Chronic infections[edit] The lungs of individuals with cystic fibrosis are colonized and infected by bacteria from an early age. These bacteria, which often spread among individuals with CF, thrive in the altered mucus, which collects in the small airways of the lungs. This mucus leads to the formation of bacterial microenvironments known as biofilms that are difficult for immune cells and antibiotics to penetrate. Viscous secretions and persistent respiratory infections repeatedly damage the lung by gradually remodeling the airways, which makes infection even more difficult to eradicate. In the initial stage, common bacteria such as S. Pseudomonas can develop special characteristics that allow the formation of large colonies, known as "mucoid" Pseudomonas, which are rarely seen in people who do not have CF. As a result, individuals with CF are now routinely isolated from one another in the healthcare setting, and healthcare providers are encouraged to wear gowns and gloves when examining patients with CF to limit the spread of virulent bacterial strains. In addition, the prolonged therapy with antibiotics and the use of corticosteroid treatments may also facilitate fungal growth. Although the clinical relevance of the fungal airway colonization is still a matter of debate, filamentous fungi may contribute to the local inflammatory response and therefore to the progressive deterioration of the lung function, as often happens with allergic bronchopulmonary aspergillosis â€” the most common fungal disease in the context of CF, involving a Th2-driven immune response to Aspergillus species. The newborn screen initially measures for raised blood concentration of immunoreactive trypsinogen. In many cases, a parent makes the diagnosis because the infant tastes salty. Due to these false positives , CF screening in newborns can be controversial. Therefore, most individuals are diagnosed after symptoms e. The most commonly used form of testing is the sweat test. Sweat testing involves application of a medication that stimulates sweating pilocarpine. To deliver the medication through the skin, iontophoresis is used, whereby one electrode is placed onto the applied medication and an electric current is passed to a separate electrode on the skin. The resultant sweat is then collected on filter paper or in a capillary tube and analyzed for abnormal amounts of sodium and chloride. People with CF have increased amounts of them in their sweat. In contrast, people with CF have less thiocyanate and hypothiocyanite in their saliva [66] and mucus Banfi et al. In the case of milder forms of CF, transepithelial potential difference measurements can be helpful. Testing is typically performed first on one or both parents and, if the risk of CF is high, testing on the fetus is performed. The American College of Obstetricians and Gynecologists recommends all people thinking of becoming pregnant be tested to see if they are a carrier. If testing shows that parent is a CFTR gene mutation carrier, the other parent is tested to calculate the risk that their children will have CF. CF can result from more than a thousand different mutations. If a family has a known uncommon mutation, specific screening for that mutation can be performed. Because not all known mutations are found on current tests, a negative screen does not guarantee that a child will not have CF. However, chorionic villus sampling has a risk of fetal death of one in and amniocentesis of one in ; [72] a recent study has indicated this may be much lower, about one in 1, The management of CF has improved significantly over the past 70 years. While infants born with it 70 years ago would have been unlikely to live beyond their first year, infants today are likely to live well into adulthood. Recent advances in the treatment of cystic fibrosis have meant that individuals with cystic fibrosis can live a fuller life less encumbered by their condition. The cornerstones of management are the proactive treatment of airway infection , and

encouragement of good nutrition and an active lifestyle. At best, current treatments delay the decline in organ function. Because of the wide variation in disease symptoms, treatment typically occurs at specialist multidisciplinary centers and is tailored to the individual. Targets for therapy are the lungs, gastrointestinal tract including pancreatic enzyme supplements , the reproductive organs including assisted reproductive technology , and psychological support. Intravenous , inhaled , and oral antibiotics are used to treat chronic and acute infections. Mechanical devices and inhalation medications are used to alter and clear the thickened mucus. These therapies, while effective, can be extremely time-consuming. Antibiotics[edit] Many people with CF are on one or more antibiotics at all times, even when healthy, to prophylactically suppress infection. This prolonged therapy often necessitates hospitalization and insertion of a more permanent IV such as a peripherally inserted central catheter or Port-a-Cath. Inhaled therapy with antibiotics such as tobramycin , colistin , and aztreonam is often given for months at a time to improve lung function by impeding the growth of colonized bacteria. All these factors related to the antibiotics use, the chronicity of the disease, and the emergence of resistant bacteria demand more exploration for different strategies such as antibiotic adjuvant therapy. This "percussive effect" can be administered also through specific devices that device chest wall oscillation or intrapulmonary percussive ventilator. Other methods such as biphasic cuirass ventilation , and associated clearance mode available in such devices, integrate a cough assistance phase, as well as a vibration phase for dislodging secretions. These are portable and adapted for home use. Chest physiotherapy is beneficial for short-term airway clearance. This effect is provided by devices that consists of a mask or a mouthpiece in which a resistance is applied only on the expiration phase. Individuals with CF may need to wear special masks at night to help push air into their lungs. These machines, known as bilevel positive airway pressure BiPAP ventilators, help prevent low blood oxygen levels during sleep. Non-invasive ventilators may be used during physical therapy to improve sputum clearance. If this is necessary many times, lung function is severely reduced. Although single lung transplantation is possible in other diseases, individuals with CF must have both lungs replaced because the remaining lung might contain bacteria that could infect the transplanted lung. Treatment of pancreatic insufficiency by replacement of missing digestive enzymes allows the duodenum to properly absorb nutrients and vitamins that would otherwise be lost in the feces.

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7: Liver Disease in Cystic Fibrosis: an Update

Cystic fibrosis (CF) is the most common genetic disease in Caucasians. As our understanding and management of children with CF continues to improve, complications from cystic fibrosis liver disease (CFLD) are becoming more common.

Inflamed nasal passages or a stuffy nose Digestive signs and symptoms The thick mucus can also block tubes that carry digestive enzymes from your pancreas to your small intestine. The result is often: Foul-smelling, greasy stools Poor weight gain and growth Intestinal blockage, particularly in newborns meconium ileus Severe constipation Frequent straining while passing stool can cause part of the rectum â€" the end of the large intestine â€" to protrude outside the anus rectal prolapse. When this occurs in children, it may be a sign of cystic fibrosis. Parents should consult a physician knowledgeable about cystic fibrosis. Rectal prolapse in children may sometimes require surgery. Rectal prolapse in children with cystic fibrosis is less common than it was in the past, which may be due to earlier testing, diagnosis and treatment of cystic fibrosis. When to see a doctor If you or your child has symptoms of cystic fibrosis â€" or if someone in your family has cystic fibrosis â€" talk with your doctor about testing for the disease. Seek immediate medical care if you or your child has difficulty breathing. Request an Appointment at Mayo Clinic Causes In cystic fibrosis, a defect mutation in a gene changes a protein that regulates the movement of salt in and out of cells. The result is thick, sticky mucus in the respiratory, digestive and reproductive systems, as well as increased salt in sweat. Many different defects can occur in the gene. The type of gene mutation is associated with the severity of the condition. Children need to inherit one copy of the gene from each parent in order to have the disease. However, they will be carriers and possibly pass the gene to their own children. Risk factors Family history. Because cystic fibrosis is an inherited disorder, it runs in families. Although cystic fibrosis occurs in all races, it is most common in white people of Northern European ancestry. Complications Respiratory system complications Damaged airways bronchiectasis. Cystic fibrosis is one of the leading causes of bronchiectasis, a condition that damages the airways. This makes it harder to move air in and out of the lungs and clear mucus from the airways bronchial tubes. Thick mucus in the lungs and sinuses provides an ideal breeding ground for bacteria and fungi. People with cystic fibrosis may often have sinus infections, bronchitis or pneumonia. Growths in the nose nasal polyps. Because the lining inside the nose is inflamed and swollen, it can develop soft, fleshy growths polyps. Coughing up blood hemoptysis. Over time, cystic fibrosis can cause thinning of the airway walls. As a result, teenagers and adults with cystic fibrosis may cough up blood. This condition, in which air collects in the space that separates the lungs from the chest wall, also is more common in older people with cystic fibrosis. Pneumothorax can cause chest pain and breathlessness. Over time, cystic fibrosis can damage lung tissue so badly that it no longer works. Lung function usually worsens gradually, and it eventually can become life-threatening. People with cystic fibrosis may experience worsening of their respiratory symptoms, such as coughing and shortness of breath, for several days to weeks. This is called an acute exacerbation and requires treatment in the hospital. Digestive system complications Nutritional deficiencies. Thick mucus can block the tubes that carry digestive enzymes from your pancreas to your intestines. The pancreas produces insulin, which your body needs to use sugar. Cystic fibrosis increases the risk of diabetes. Around 30 percent of people with cystic fibrosis develop diabetes by age The tube that carries bile from your liver and gallbladder to your small intestine may become blocked and inflamed, leading to liver problems and sometimes gallstones. Intestinal obstruction can happen to people with cystic fibrosis at all ages. Children and adults with cystic fibrosis are more likely than are infants to develop intussusception, a condition in which a section of the intestines folds in on itself like an accordion. Distal intestinal obstruction syndrome DIOS. DIOS is partial or complete obstruction where the small intestine meets the large intestine. Reproductive system complications Almost all men with cystic fibrosis are infertile because the tube that connects the testes and prostate gland vas deferens is either blocked with mucus or missing entirely. Certain fertility treatments and surgical procedures sometimes make it possible for men with cystic fibrosis to become biological fathers. Still, pregnancy can worsen the signs and symptoms of cystic fibrosis, so be sure to discuss the possible risks

with your doctor. Other complications Thinning of the bones osteoporosis. People with cystic fibrosis are at higher risk of developing a dangerous thinning of bones. Electrolyte imbalances and dehydration. Because people with cystic fibrosis have saltier sweat, the balance of minerals in their blood may be upset. Signs and symptoms include increased heart rate, fatigue, weakness and low blood pressure. Prevention If you or your partner has close relatives with cystic fibrosis, you both may want to undergo genetic testing before having children. The test, which is performed in a lab on a sample of blood, can help determine your risk of having a child with cystic fibrosis. Before you decide to be tested, you should talk to a genetic counselor about the psychological impact the test results might carry.

8: Cystic fibrosis - Symptoms and causes - Mayo Clinic

Cystic fibrosis (CF)-related liver disease (CFLD) is a common symptom in patients with CF. However, its prevalence, risk factors, and evolution are unclear. We analyzed a large database of patients with CF to investigate the incidence of CFLD, its related risk factors, and the use and effect of ursodeoxycholic acid (UDCA) treatment.

9: Researchers ID Risk Factors of Advanced Liver Disease in Cystic Fibrosis Patients | RT

Liver disease in people with cystic fibrosis is likely caused by abnormally thick fluids in the liver. Cystic fibrosis results in decreased fluid flow, thereby increasing the concentration of bile components and contributing to the abnormal fluid thickness in the liver.

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