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Choledochal Cyst: Review of the Literature on Etiology and a Representative Case Study

A thesis submitted in partial fulfillment of the requirements for the degree of Bachelor of Science in Biology and the Honors Program

by

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May, 2012
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May 2012
Abstract

Choledochal cysts are fluid-filled dilations of the common bile duct or hepatic duct, which currently have an unknown etiology (Singham, Yoshida and Scudamore, 2009). The current ideas of the etiology signify that choledochal cysts are caused by a reflux of pancreatic juices into the common bile duct, which causes increased expression of matrix metalloproteinase-1 and -2 and the formation of protein plugs (Babbitt, Starshak and Clemett, 1973; Mao, Tang and Ruan, 2008; Kaneko et al., 2007). The combination of these events causes increased intraluminal pressure and, consequently, cyst formation (Babbitt, Starshak and Clemett, 1973; Mao, Tang and Ruan, 2008; Kaneko et al., 2007).

A case study of a 5 day old patient diagnosed with a choledochal cyst is discussed in order to raise the awareness of choledochal cysts as a cause of cholestatic jaundice in infants.
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Introduction

Etiology

Choledochal cysts are fluid-filled dilations of the common bile duct or hepatic duct (see figure 1) (Singham, Yoshida and Scudamore, 2009). Approximately 90% of choledochal cysts occur with an anomalous pancreaticobiliary duct maljunction (Singham, Yoshida and Scudamore, 2009). Anomalous pancreaticobiliary duct maljunction occurs when the pancreatic duct joins with the common bile duct 1 cm or more before the duodenum (Miyano and Yamataka, 1997). This maljunction of the common bile duct and pancreatic duct allows for the regurgitation of pancreatic juices into the common bile duct, which is believed to play a role in the pathogenesis of choledochal cysts (Babbitt, Starshak and Clemett, 1973). However, this theory does not take into account those cases of choledochal cysts that occur in the absence of an anomalous pancreaticobiliary duct maljunction, which is why the etiology of choledochal cysts is believed to be multifactorial.
Figure 1. A comparison of a typically developed pancreaticobiliary junction and a pancreaticobiliary duct maljunction that occurs with a choledochal cyst. Note the junction of the common duct and the chief pancreatic duct is more distal to the duodenum in a patient with a choledochal cyst than it is in a patient that has a typically developed pancreaticobiliary junction. Also note the presence of a cystic dilation of the common bile duct in the figure representing a choledochal cyst. Image from Donald Babbitt et al., "Choledochal Cyst: A Concept of Etiology" (American Journal of Roentgenology, Radium Therapy, and Nuclear Medicine 119.1, 1973) 57-62. Print.

There are two common theories about the etiology of choledochal cysts. Babbitt’s theory states that cysts are caused by the reflux of pancreatic juices into the common bile duct due to the presence of an abnormal pancreaticobiliary duct maljunction (Babbitt, Starshak and Clemett, 1973). This theory, however, does not take into account those cases of choledochal cysts that occur without the presence of anomalous pancreaticobiliary duct maljunction. Davenport and Basu (2005) suggest that choledochal cysts are caused by an over-proliferation of epithelial cells during the
embryogenesis of the common bile duct. No theory has been proposed that fully explains the pathogenesis of choledochal cysts.

**Classification**

Choledochal cysts are classified as follows: type I is a dilation of either a portion of or the entire common bile duct; type II is a diverticulum projecting from the common bile duct; type III is a dilation of the junction of the common bile duct and the duodenum or of the common bile duct and the pancreatic duct; type IVa consists of multiple cysts of the intra- and extrahepatic ducts; type IVb consists of multiple cysts of only the extrahepatic ducts; type V is a dilation of the intrahepatic ducts (see figure 2) (Todani et al., 1977). Lilly, Stellin, and Karrer (1985) have described patients with choledochal cyst-like symptoms, such as obstructive jaundice and abdominal pain, but without the actual cyst present. These patients exhibited the same histology of the common bile duct as patients with actual cystic dilations, and, because of the similarities of the symptoms and histology of these patients to that of patients with actual cystic dilations of the common bile duct, Lilly et al. (1985) termed this condition a “form fruste” choledochal cyst.
Presentation

The presentation of choledochal cysts varies widely based on age, but most cases of choledochal cysts present with one or more symptoms from the classic triad: pain in the upper right quadrant, jaundice, and a mass in the upper right quadrant (Singham, Yoshida and Scudamore, 2009). Patients under the age of one typically present with jaundice and acholic stools (Vijayaraghavan et al., 2006). Patients between one and twelve years of age typically present with pain and jaundice (Vijayaraghavan et al., 2006). In adults with choledochal cysts, upper right quadrant pain, nausea, and vomiting are the most common findings (Wiseman et al., 2005).

Epidemiology

The epidemiology of choledochal cysts is peculiar. The prevalence of choledochal cysts in the western countries is very low; between 1 in 100,000 and 1 in 150,000
individuals develop choledochal cysts (Lipsett and Pitt, 2003). However, in Asia, the prevalence is much higher; approximately 1 in 1000 individuals develop choledochal cysts in Asia (Lipsett and Pitt, 2003). Choledochal cysts also occur in women around 75% to 80% more often than they do in men (Lipsett and Pitt, 2003). Choledochal cysts can present from the prenatal stage to adulthood, but two-thirds of choledochal cysts present before the age of ten (Singham, Yoshida and Scudamore, 2009). The epidemiology of choledochal cysts could offer a great amount of insight into the etiology of the disease. By isolating the differences between the populations that have a higher risk of becoming diagnosed with choledochal cysts and those that do not, the cause of the disease might be elucidated.

**Treatment**

The treatment of choledochal cysts has evolved since their discovery, but the most widely accepted treatment today is the excision of the cyst with a Roux-en-Y hepaticojujenostomy (see figure 3) (Shimotakahara et al., 2005). This procedure involves a complete removal of the cyst followed by connecting the jejunum portion of the small intestine to the common hepatic duct and connecting the duodenum portion of the small intestine to the jejunum (Shimotakahara et al., 2005). This method is particularly successful because it prevents post-operative complications, such as gastric bile reflux, which can lead to cholangiocarcinoma (Shimotakahara et al., 2005). This method is also more commonly performed in a minimally invasive laparoscopic, or “keyhole,” fashion in Asia, which aims to decrease patient post-operative pain, risk of infection, cosmetic
consequences, and recovery time when compared to open abdomen surgery (Gupta et al., 2009).

Figure 3. Representation of a Roux-en-Y hepaticojejunostomy. Image from CPMC Sutter Health; Management of Bile Duct Problems Procedure Profile; CPMC, 2011; Web; 04 Feb. 2011.

Malignance

Kasai, Asakura, and Taira (1970) were the first to report that choledochal cysts lead to an increased incidence of malignance compared to the incidence in patients without choledochal cysts. Malignant change in patients with choledochal cysts is thought to occur due to inflammation of the biliary tract caused by the cholangitis that is associated with choledochal cysts, the mixing of pancreatic juices and bile, or cholestasis (Bismuth and Krissat, 1999; Holzinger, Z'Graggen and Buchler, 1999; Singham, Yoshida and Scudamore, 2009). This chronic inflammation leads to dysplasia of the common bile duct and destruction of the
mucin-secreting cells of the common bile duct (Bismuth and Krissat, 1999; Singham, Yoshida and Scudamore, 2009). Inflammation of the common bile duct causes immune cells to secrete carcinogenic compounds into the inflamed cells, which, under normal conditions, are discarded by the cell (Holzinger, Z'Graggen and Buchler, 1999). However, in cholangiocarcinoma, the mechanisms for disposing of these carcinogens are defective (Holzinger, Z'Graggen and Buchler, 1999). The reflux of pancreatic juices into the common bile duct is also thought to cause K-ras mutations and overexpression of p53 (Holzinger, Z'Graggen and Buchler, 1999; Singham, Yoshida and Scudamore, 2009). Both K-ras mutations and overexpression of p53 in the common bile duct can lead to a cancerous state in the common bile duct (Holzinger, Z'Graggen and Buchler, 1999; Singham, Yoshida and Scudamore, 2009).

The malignant cells of the common bile duct that originate at the choledochal cyst can spread in the common bile duct past the noticeable borders of the choledochal cyst (Holzinger, Z'Graggen and Buchler, 1999). For this reason, complete excision of the choledochal cyst does not eliminate the chance of cancer of the common bile duct (Holzinger, Z'Graggen and Buchler, 1999). Consequently, life-long observation of a patient after excision of a choledochal cyst is recommended (Holzinger, Z'Graggen and Buchler, 1999).

**Purpose**

This study into choledochal cysts may help to eliminate some unknowns in the etiology of choledochal cysts by amalgamating the current ideas about the
etiology and providing a unifying theory. This study also aims to increase the awareness of choledochal cysts as a possible cause of jaundice in infants, even though the disease is relatively rare.
**Historical Background**

**Evolution of the Classification**

Vater and Ezler were the first people to publish a description of the anatomical structure of a choledochal cyst in 1723 (Lipsett et al., 1994). In 1852, Douglas (1852) published the first well-documented report of a choledochal cyst in one of his patients, who presented with the classical triad of symptoms. After Douglas’s report, multiple types of choledochal cysts were discovered, and, in 1959, Alonso-Lej, Rever Jr., and Pessagno (1959) devised a three class system for classifying the biliary abnormalities by classifying choledochal cysts as type I, which is a dilation of part of or the entire common bile duct, type II, which is a diverticulum off of the common bile duct, and type III, which is a dilation of the junction of the common bile duct and the duodenum or of the common bile duct and the pancreatic duct and is termed a choledochocele. In 1958, Caroli et al. (1958) described a fourth type of choledochal cyst, which consisted of dilations of the intrahepatic ducts, and, in 1977, Todani et al. (1977) developed the current five class classification system of choledochal cysts by adding two classes of choledochal cysts to the system devised by Alonso-Lej et al. (1959). The classes added to the Alonso-Lej system were type IVa and IVb, which consist of multiple cysts of the intra- and extrahepatic ducts and multiple cysts of only the extrahepatic ducts, respectively, and type V, which is the choledochal cyst discovered by Caroli et al. (1958) (Todani et al., 1977). In 2004, Visser et al. (2004) proposed the rejection of the Todani classification system because Visser et al. hypothesized that the different types of choledochal cysts are distinct diseases with different pathogeneses. Visser et al. (2004)
suggested that choledochal cysts should be classified using a system that refers to each type of choledochal cyst using descriptive terms. Visser et al. (2004) also suggested that type I and IV cysts are actually the same disease because Visser et al. asserted that dilation of the intrahepatic ducts is always present with type I choledochal cysts, but to a varying degree. Visser et al. (2004) proposed replacing the Todani classification system with the following four class system: Type I and IV would be encompassed in a type called choledochal cyst, type II would be renamed choledochal diverticulum, type III would be termed choledochocele, and type V would be named Caroli Disease. However, this classification system has yet to be widely accepted.

**Evolution of the Treatment**

Douglas (1852), who published the first documented case of a choledochal cyst, treated his patient by draining the cyst with a trocar, treating the area with hot compresses, and prescribing the patient laxatives. However, Douglas’s patient died six months after entering into his care (Douglas, 1852). The first accepted treatment of choledochal cysts was marsupialization, which involved creating a slit into the cyst and suturing the cyst in a way that allowed the cyst to drain freely into the abdominal cavity (Kasai, Asakura and Taira, 1970). Marsupialization was quickly abandoned due to the high mortality rate associated with this procedure (Kasai, Asakura and Taira, 1970). In 1953, Gross (1953) outlined a treatment that involved internal drainage of the cyst along with a Roux-en-Y cystoduodenostomy or cystojejunostomy procedure. However, the procedure devised by Gross (1953) only temporarily relieved the symptoms; the patients later returned with the same symptoms because the cyst continually refilled with fluid,
which left the patient vulnerable to cholangitis and cholangiocarcinoma (Kasai, Asakura and Taira, 1970). Golder Lewis McWhorter (1924) performed the first surgical removal of a choledochal cyst in 1924 by excising the cyst and creating an anastomosis between the common hepatic duct and the duodenum. McWhorter (1924) argued that the excision of the choledochal cyst offered the best option for treatment because excision better prevented the recurrence of symptoms and offered the best prognosis for the patient. However, internal drainage of the cyst remained the favored method of treatment of choledochal cysts because surgical technique at the time caused high mortality rates in patients that had complete excision of the cyst (Kasai, Asakura and Taira, 1970). From 1981 to 1983, after surgical technique improved, the excision of the choledochal cyst and the creation of an anastomosis between the common bile duct and the jejunum became the dominant form of treatment of choledochal cysts (Kasai, Asakura and Taira, 1970). This procedure was replaced as the favored method of treatment of choledochal cysts in 1984 by the Roux-en-Y hepaticojejunostomy because the Roux-en-Y hepaticojejunostomy allows the bile to empty into the duodenum, which is the normal physiological site of entry (see figure 3) (Kasai, Asakura and Taira, 1970). This procedure remains the favored treatment of choledochal cysts today (Shimotakahara et al., 2005).
Literature Review

Babbitt’s Hypothesis

The most widely accepted theory about the etiology of choledochal cysts is Babbitt’s hypothesis (Babbitt, Starshak and Clemett, 1973). Babbitt, Starshak, and Clemett (1973) note the preponderance of anomalous pancreaticobiliary duct maljunction in patients with choledochal cysts. Babbitt et al. (1973) theorize that this maljunction allows for the regurgitation of pancreatic juices into the common bile duct. The pressure within the pancreatic duct is 22.1mmHg to 36.8mmHg, and the pressure in the common bile duct is 18.4mmHg to 22.1mmHg (Babbitt, Starshak and Clemett, 1973). Because fluid flows from higher pressure to lower pressure, fluid leaving the pancreatic duct regurgitates into the common bile duct (Babbitt, Starshak and Clemett, 1973). During normal development of the pancreaticobiliary junction, a sphincter forms to prevent this regurgitation; however, in patients with choledochal cysts, no sphincter is present to prevent this regurgitation of pancreatic juices into the common bile duct (Babbitt, Starshak and Clemett, 1973). This hypothesis that regurgitation of pancreatic juices causes choledochal cysts is supported by the fact that the fluid found in choledochal cysts is high in amylase content, a component of pancreatic juices (Babbitt, Starshak and Clemett, 1973). With Babbitt’s hypothesis in mind, Joseph, Fonkalsrud, and Longmire (1965) propose that this regurgitation of pancreatic juices causes thickening of the wall of the common bile duct due to repeated incidences of cholangitis caused by a bacterial infection of the common bile duct due to the blockage of the common bile duct by the cyst.
The importance of the anomalous pancreaticobiliary duct maljunction in the etiology of choledochal cysts is also illustrated by an experiment in which Ohkawa et al. (1981) created a model of anomalous pancreaticobiliary duct maljunction in dogs. The creation of this anomalous pancreaticobiliary duct maljunction is done by performing a pancreaticocholecystostomy or a pancreaticocholedochostomy (Ohkawa et al., 1981). Both procedures result in cystic dilation of the common bile duct that is analogous to choledochal cysts in humans (Ohkawa et al., 1981). The cystic dilation is associated with pancreatic reflux into the common bile duct in both procedures, which is evidenced by the presence of amylase in the bile (Ohkawa et al., 1981). These findings offer further support of Babbitt’s hypothesis.

**Incorporation of New Ideas into Babbitt’s Hypothesis**

The presence of pancreatic juices in choledochal cysts has been looked at by many as the possible cause of choledochal cysts. However, unlike Babbitt et al. (1973), Kato, Asakura, and Kasai (1974) believe that the pancreatic juices might not directly cause the pathology noted in choledochal cysts. Kato et al. (1974) assert that both structural weakness of the common bile duct and intraluminal pressure are necessary to produce surgically induced cystic dilations of the common bile duct in dogs.

Kaneko et al. (2007) report a hypothesis for the etiology of choledochal cysts that incorporates increased intraluminal pressure and reflux of pancreatic juices into the common bile duct. The pancreatic juice in choledochal cysts contains, among other things, activated trypsin and lithostathine (Kaneko et al., 2007). Kaneko et al. (1974) theorize that protein plugs are present in as much as 40% of cases of choledochal cysts.
Protein plugs are solid masses of protein that obstruct the bile duct and pancreatic duct (Kaneko et al., 2007). This blockage of the ducts leads to an increase in intraductal pressure and the resulting symptoms of choledochal cysts (Kaneko et al., 2007). These protein plugs are composed predominately of lithostathine (Kaneko et al., 2007). Lithostathine is secreted in a soluble form by the pancreas; however, the purpose of lithostathine secretion is currently unknown (Kaneko et al., 2007). Trypsinogen, also secreted by the pancreas, is cleaved to produce its active form, trypsin, in order to digest proteins in the small intestine (Kaneko et al., 2007). However, trypsin also cleaves lithostathine into lithostathine S1 (Kaneko et al., 2007). Lithostathine S1 is insoluble and is the primary component of protein plugs (Kaneko et al., 2007). Because of these findings, Kaneko et al. (2007) suggest that anomalous pancreaticobiliary duct maljunction allows pancreatic juices to regurgitate into the common bile duct, which, by an unknown mechanism, causes the cleavage of trypsinogen into trypsin. Consequently, trypsin cleaves the soluble form of lithostathine into the insoluble form, which flows down the common bile duct and aggregates to form an obstructive protein plug (see figure 4) (Kaneko et al., 2007).
Figure 4. Hypothesized mechanism of protein plug formation in choledochal cysts. Image from Kaneko, K., et al., "Proteomic Analysis of Protein Plugs: Causative Agent of Symptoms in Patients with Choledochal Cyst." (Digestive Diseases and Sciences Vol. 52.8. 2007) 1979-86. Print.

The description of protein plug formation by Kaneko et al. (2007) supports the findings of Turowski, Knisely, and Davenport (2011), who state that pressure and not pancreatic reflux causes the pathology found in choledochal cysts. Turowski et al. (2011) hypothesize that there is an inverse correlation between amylase concentration in the bile and pressure in the choledochal cyst. Turowski et al. (2011) also assert that epithelial and morphological pathology in choledochal cysts is positively correlated with choledochal cyst pressure and not with bile amylase concentration, which challenges the ideas of Babbitt et al. (1973).

Mao, Tang, and Ruan (2008) offer a connection between the hypothesis formulated by Babbitt et al. (1973) that the pathology of choledochal cysts is caused by
regurgitated pancreatic juices and the findings of Turowski et al. (2011) that suggest that the pathology of choledochal cysts is predominately due to the increased intraductal pressure in patients with choledochal cysts. Mao et al. (2008) theorize that matrix metalloproteinase-1 and -2 are over expressed in the wall of the choledochal cyst compared to that of the gallbladder of a patient with a choledochal cyst and that of the common bile duct in a patient without a choledochal cyst. Matrix metalloproteinases act to break down the extracellular matrix, which is important for the development and maintenance of the biliary tract (Mao, Tang and Ruan, 2008). However, overexpression of matrix metalloproteinase-1 and -2 causes an increased break down of the extracellular matrix, which could lead to a weakening of the wall of the biliary tract (Mao, Tang and Ruan, 2008). This weakening of the wall could lead to the formation of a cyst in the presence of high intraductal pressure (Mao, Tang and Ruan, 2008). Mao et al. (2008) also assert that the regurgitation of the pancreatic juices into the common bile duct can stimulate the epithelial cells of the duct to increase expression of the matrix metalloproteinase-1 and -2.
Case Study

The following is a case study about a 5-day-old, Japanese female who was brought to the doctor’s office because she developed jaundice and acholic stools. The purpose of this case study is to bring to light the possible causes of these symptoms beyond the more common non-cholestatic causes, such as neonatal jaundice and breast milk jaundice.

Jennifer Chang

Chief Complaint

Jennifer Chang is a 5-day-old, Japanese female. Jennifer is brought into the doctor’s office after she developed jaundice and acholic stools the previous evening.

History of Present Illness

Jennifer’s mother received no prenatal care, but insisted that she took good care of her baby while she was pregnant. Jennifer’s mother denies drinking, smoking, or using drugs during pregnancy. Jennifer’s mother spontaneously went into labor, and Jennifer was delivered vaginally after 5 hours of labor at a gestational age of 39 weeks. There were no complications during delivery. Jennifer’s mother was given an epidural before giving birth. Jennifer’s 1-minute APGAR score was a 9, with one point being lost due to acrocyanosis. After treating her with oxygen, Jennifer’s 5-minute APGAR score was a 10. Jennifer and her mother were released from the hospital the next day. Jennifer’s mother states that Jennifer is nursing around 9 times a day and has regular bowel movements, which were brown until they started becoming pale in color last night. Jennifer’s mother said that Jennifer started becoming jaundiced last night. However, Jennifer’s grandmother told Jennifer’s mother that jaundice in newborns is normal, so
Jennifer’s mother took Jennifer in to see the doctor this morning instead of taking her to the E.R. last night. Jennifer’s mother says that Jennifer was fussy last night and that Jennifer still seems fussy this morning.

**Social and Family History**

Jennifer’s mother states that she and her boyfriend, Jennifer’s father, are in between jobs, but just got health insurance for Jennifer. Jennifer is living with her parents in her maternal grandparents’ house. This is Jennifer’s mother’s first pregnancy and delivery, and this pregnancy was unintended but welcomed. Jennifer’s mother was healthy during her pregnancy. Jennifer’s mother states that the only family history of illness is heart disease on the maternal side of the family and skin cancer and diabetes on the paternal side. Jennifer’s mother states that there is no history of liver disease in the family.

**Physical Exam**

Jennifer’s vital signs, as recorded by the nurse, are as follows:

Length: 19.5”    Weight: 7 lbs. 8 oz.    Head Circumference: 13.75”    BP: 76/46

Temp: 99.1°F    RR: 45    HR: 143

Physical exam findings for Jennifer Chang:

**General:**

Appears ill, but attentive. Appears irritable.

**Skin:**

Skin is soft and smooth, but jaundiced. Skin is well perfused. Mongolian spot present in the lower lumbar region.

**Head:**

Anterior fontanelle is soft and flat. Skull is symmetrical. Head circumference is within normal range.

**Face:**

Face is symmetrical. No abnormal facies. Negative Chvostek’s sign.
Eyes: Pupils are round and reactive to light. Scleras are jaundiced. Red reflex present. Corneal reflex present. Cornea and lens are clear.

Ears: Ears are normal in size, shape, and position. Tympanic membrane visible with diffuse light reflex. Acoustic blink reflex present.

Nose: Both nostrils patent. Nasal septum is midline.

Mouth: Alveolar ridges normal. Upper hard palate is intact with no cleft present. Tongue is pink and normal in size. Tonsils could not be visualized.


Chest/Lungs: No nasal flaring. No grunting, wheezing, stridor, or obstruction. Chest movement is symmetrical. No retractions present. No tactile fremitus noted. No crackles, wheezes, or rhonchi upon auscultation.

Heart: No cyanosis. Regular rate and rhythm. Radial, carotid, femoral, Dorsalis pedis easily palpable bilaterally. Normal S1, S2. No murmurs, rubs, or gallops.

Abdomen: No swelling or redness of umbilicus or area surrounding umbilicus. No distension. No hepatosplenomegaly. Bowel sounds present in all 4 quadrants. No masses noted upon palpation.

Genitals: Labia and clitoris normal in size. Hymen and vaginal opening present.

Neurological: Cranial nerves 2-12 grossly intact. Tone is normal. Knee, ankle, biceps, Moro, stepping, rooting, suck, palmar, and plantar reflexes are present and symmetrical.

Laboratory and Imaging Findings

Jennifer’s laboratory results:

**Complete Blood Count**

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<th>Value</th>
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</tr>
<tr>
<td>Hemoglobin</td>
<td>13.5g/dL</td>
</tr>
<tr>
<td>Hematocrit</td>
<td>44.4%</td>
</tr>
<tr>
<td>MCV</td>
<td>108.3fL</td>
</tr>
<tr>
<td>MCH</td>
<td>32.9pg</td>
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<tr>
<td>MCHC</td>
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<tr>
<td>RDW</td>
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</tr>
<tr>
<td>White Cell Count</td>
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<tr>
<td>Neutrophil Count (Absolute)</td>
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<tr>
<td>Neutrophil Count (Relative)</td>
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<td>Lymphocyte (Absolute)</td>
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<td>Lymphocyte (Relative)</td>
<td>41.6%</td>
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<td>Monocyte Count (Absolute)</td>
<td>0.5 x10^{9}/L</td>
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<td>Monocyte Count (Relative)</td>
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<td>Eosinophil Count (Absolute)</td>
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<tr>
<td>Eosinophil Count (Relative)</td>
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<tr>
<td>Basophil Count (Absolute)</td>
<td>0.02 x10^{9}/L</td>
</tr>
<tr>
<td>Test</td>
<td>Result</td>
</tr>
<tr>
<td>-------------------------------</td>
<td>-------------</td>
</tr>
<tr>
<td>Basophil Count (Relative)</td>
<td>0.2%</td>
</tr>
<tr>
<td>Platelet Count</td>
<td>244 x10⁹/L</td>
</tr>
<tr>
<td>MPV</td>
<td>8.3fL</td>
</tr>
<tr>
<td><strong>Liver Function Tests</strong></td>
<td></td>
</tr>
<tr>
<td>ALT</td>
<td>60U/L</td>
</tr>
<tr>
<td>ALP</td>
<td>450U/L</td>
</tr>
<tr>
<td>AST</td>
<td>95U/L</td>
</tr>
<tr>
<td>γGT</td>
<td>290U/L</td>
</tr>
<tr>
<td>Total Bilirubin</td>
<td>15.3mg/dL</td>
</tr>
<tr>
<td>Conjugated Bilirubin</td>
<td>10.1mg/dL</td>
</tr>
<tr>
<td>Albumin</td>
<td>22g/L</td>
</tr>
<tr>
<td><strong>Glucose</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>89mg/dL</td>
</tr>
<tr>
<td><strong>Prothrombin Time</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>10.9s</td>
</tr>
<tr>
<td><strong>α-1 Antitrypsin</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>180mg/dL</td>
</tr>
<tr>
<td><strong>Cholesterol</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>163mg/dL</td>
</tr>
<tr>
<td><strong>Urine Reducing Substances</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Negative</td>
</tr>
</tbody>
</table>
Jennifer’s abdominal ultrasound results:

There is a dilation of the common bile duct. The gall bladder appears contracted.

There is communication between the cystic duct and the dilation of the common bile duct.
Jennifer’s HIDA scan results:

Hepatic uptake at 5 minutes. Filling of gall bladder and choledochal cyst after 1 hour. No intestinal activity after 5 hours.

Diagnosis and Treatment

Jennifer Chang is diagnosed with a type I choledochal cyst with complete obstruction of bile flow based on the lab results, abdominal ultrasound, and HIDA scan. Jennifer’s mother is informed of the diagnosis, and Jennifer’s doctor proceeds with the immediate excision of the choledochal cyst with a Roux-en-Y hepaticojujenostomy. After Jennifer’s discharge, her mother is told to bring Jennifer in for a follow-up appointment in four days or sooner if Jennifer’s jaundice returns.
Follow-up

Four days after Jennifer’s discharge from the hospital, Jennifer comes in for blood work and follow-up. She shows no signs of cholestasis. She appears less irritable than before surgery, and her mother says that she has not been fussy. The incision site is healing well and shows no signs of infection or tenderness. Jennifer’s mother is instructed to bring Jennifer in if Jennifer’s symptoms recur and every year for blood work to ensure that there is no recurrence of symptoms due to recurrence of the cyst, stricture of the anastomosis, or presence of cholangiocarcinoma.
Case Study Description

Presentation

Choledochal cysts may present in many forms primarily depending on age (Singham, Yoshida and Scudamore, 2009; Vijayaraghavan et al., 2006; Wiseman et al., 2005). This case study refers to a 5 day old female with a type I choledochal cyst. The patient is Japanese, which correlates with the increased incidence of choledochal cysts among patients of Asian descent (Lipsett and Pitt, 2003). Because of the patient’s age, the patient’s underlying symptoms were jaundice and acholic stools (Vijayaraghavan et al., 2006). Jaundice occurs in patients with choledochal cysts because choledochal cysts cause an obstruction of the common bile duct, which mechanically inhibits the excretion of bilirubin (Iyanagi, Emi and Ikushiro, 1998). Jaundice created by obstruction of the biliary tract is a form of cholestatic jaundice due to the lack of clearance of bile from the biliary tract (Iyanagi, Emi and Ikushiro, 1998). Cholestatic jaundice creates a state of conjugated hyperbilirubinemia (Iyanagi, Emi and Ikushiro, 1998). Bilirubin must be conjugated to a molecule of glucuronic acid in order for it to be soluble in the bile; despite the prevention of excretion of bile by the obstruction of the biliary tract, the bilirubin continues to become conjugated (Iyanagi, Emi and Ikushiro, 1998). This increase in concentration of conjugated bilirubin in the bile causes conjugated bilirubin to enter the blood plasma by an unknown mechanism, which directly causes conjugated hyperbilirubinemia (Iyanagi, Emi and Ikushiro, 1998).

Acholic stools are a result of cholestatic jaundice (Iyanagi, Emi and Ikushiro, 1998). The normal brown color of stool is caused by the presence of bile salts in the stool.
Due to the lack of clearance of bile from the biliary tract, these bile salts are not deposited in the stool, which causes the stool to be pale in color (Iyanagi, Emi and Ikushiro, 1998).

Differential Diagnosis

There are many possible causes of jaundice in infants (Blackburn, 1995). Many infants develop physiological jaundice during the first few weeks of life because of the combination of the breakdown of fetal blood cells and the immaturity of the newborn liver (Blackburn, 1995). However, physiological jaundice causes unconjugated hyperbilirubinemia because unconjugated bilirubin builds up in the blood plasma due to the fact that newborns cannot conjugate bilirubin (Blackburn, 1995).

Cholestatic jaundice should always be thought of as a possibility in infants with jaundice because early recognition of cholestatic diseases is often essential in obtaining a good outcome (Moyer et al., 2004). There are many causes of cholestatic jaundice in infants; most of these causes should be considered in the differential diagnosis of jaundiced infants (Moyer et al., 2004). These causes include the following diseases: biliary atresia, choledochal cyst, Alagille syndrome, inspissated bile, gall stones, neonatal hepatitis, progressive familial intrahepatic cholestasis, and $\alpha$-1 antitrypsin deficiency (Moyer et al., 2004).

Biliary atresia is a destruction or discontinuity of the extrahepatic biliary tract (de Carvalho, Ivantes and Bezerra, 2007). Biliary atresia has a high preponderance in people of Asian descent and in females, so biliary atresia is a likely diagnosis for the patient in
this case study (de Carvalho, Ivantes and Bezerra, 2007). Biliary atresia causes a complete obstruction to the flow of bile out of the liver, which results in jaundice, acholic stools, choluria, and hepatomegaly in most patients (de Carvalho, Ivantes and Bezerra, 2007). This disease presents the same way as choledochal cysts and has the same laboratory findings as choledochal cysts, but the treatment of biliary atresia is immediate surgery to restore bile flow, which makes it important to rule this disease out as soon as possible (de Carvalho, Ivantes and Bezerra, 2007). An ultrasound should easily distinguish a choledochal cyst from biliary atresia (de Carvalho, Ivantes and Bezerra, 2007).

Alagille syndrome is a genetic disorder that presents as abnormalities in the liver, heart, eye, skeleton, facial structure, and kidneys (Turnpenny and Ellard, 2012). The liver has a paucity of intrahepatic bile ducts, which causes cholestasis and jaundice (Turnpenny and Ellard, 2012). The heart is marked by congenital heart disease in patients with Alagille syndrome (Turnpenny and Ellard, 2012). The eyes show posterior embryotoxon among other abnormalities (Turnpenny and Ellard, 2012). Patients with Alagille syndrome have butterfly vertebrae along with other skeletal abnormalities (Turnpenny and Ellard, 2012). The faces of patients with Alagille syndrome are marked by prominent forehead, deep-set eyes, depressed nasal bridge, large ears, and a prominent mandible (Turnpenny and Ellard, 2012). Many structural and functional abnormalities of the kidneys also present in patients with Alagille syndrome (Turnpenny and Ellard, 2012). However, during infancy, Alagille syndrome can present mainly as cholestatic jaundice (Turnpenny and Ellard, 2012). Alagille syndrome is diagnosed using genetic
testing to test for the presence of Jag-1 and Notch-2 mutations, which are present in patients with Alagille syndrome (Turnpenny and Ellard, 2012).

Inspissated bile is a thickening of bile, which can lead to an obstruction of the biliary tract and, thus, cholestatic jaundice (Bernstein, Braylan and Brough, 1969). This disease can produce similar laboratory results as a choledochal cyst, so ultrasound is used to distinguish the two (Bernstein, Braylan and Brough, 1969).

Gall stones are caused by a precipitation of some component of the bile (Holcomb and Holcomb, 1990). Gall stones can lead to a blockage of the biliary tract and cholestatic jaundice (Holcomb and Holcomb, 1990). Gall stones can cause similar laboratory test results as choledochal cysts, so an abdominal ultrasound is used to distinguish the two (Holcomb and Holcomb, 1990).

Idiopathic neonatal hepatitis is an infection of the liver with an unknown etiology, which causes hepatic dysfunction and, possibly, cholestatic jaundice (Lough and Metrakos, 1967). Neonatal hepatitis may cause similar laboratory findings to patients with choledochal cysts, but an abdominal ultrasound easily distinguishes the two (Gubernick et al., 2000).

Progressive familial intrahepatic cholestasis is an autosomal recessive genetic disorder in which the patient has a defect in bile formation (Hori, Nguyen and Uemoto, 2010). This defect is due to a mutation in one of three genes: familial intrahepatic cholestasis 1, bile salt export pump, or multidrug resistant 3 (Hori, Nguyen and Uemoto, 2010). Progressive familial intrahepatic cholestasis can produce similar laboratory
findings to choledochal cysts, but can be differentiated from choledochal cysts via ultrasound (Hori, Nguyen and Uemoto, 2010).

α-1 antitrypsin deficiency is a genetic disorder characterized by a defect in α-1 antitrypsin, which prevents the release of α-1 antitrypsin from liver cells and causes the death of these liver cells (Topic, Prokic and Stankovic, 2011). α-1 antitrypsin deficiency presents in infants as cholestatic jaundice (Topic, Prokic and Stankovic, 2011). α-1 antitrypsin deficiency is caused by an allele of the protease inhibitor locus on chromosome 14q32.1 that causes low serum levels of α-1 antitrypsin (Topic, Prokic and Stankovic, 2011). α-1 antitrypsin deficiency is diagnosed by a deficiency in serum α-1 antitrypsin (Topic, Prokic and Stankovic, 2011). Lab values for aspartate aminotransferase and alanine aminotransferase can also be used to differentiate between choledochal cysts and α-1 antitrypsin deficiency because aspartate aminotransferase and alanine aminotransferase are more increased in patients with α-1 antitrypsin deficiency than in patients with a choledochal cyst because α-1 antitrypsin deficiency directly causes hepatocellular damage, whereas choledochal cysts cause hepatocellular damage indirectly and to a lesser extent (Topic, Prokic and Stankovic, 2011).

History of Present Illness

Many choledochal cysts are diagnosed via a prenatal ultrasound (Wong et al. 2005). To avoid this immediate diagnosis, this patient’s mother did not have prenatal care for financial reasons. Newborns with choledochal cysts can be born without any problems and develop jaundice when complete obstruction occurs, which explains why this patient had an uncomplicated birth. The patient became jaundiced and had acholic
stools the night before she was brought to the pediatrician’s office. Also, because choledochal cysts may cause pain, the patient was acting fussy from the time that she developed her symptoms.

**Family History**

The patient had no family history of liver disease, which correlates with the fact that familial cases of choledochal cysts are very rare (Clifton et al., 2006).

**Physical Examination**

Other than jaundice and fussiness, the patient’s physical examination showed no abnormal findings.

**Laboratory Work-up**

In order to distinguish between physiological and cholestatic jaundice, the patient’s serum direct bilirubin and serum total bilirubin were tested (Moyer et al., 2004). Serum total bilirubin tests the concentration of bilirubin in the patient’s blood and serum (Moyer et al., 2004). Direct bilirubin tests the concentration of conjugated bilirubin in the patient’s blood (Moyer et al., 2004). In a patient with cholestatic jaundice, the conjugated bilirubin is elevated if it is greater than 1.0 mg/dL or more than 20% of the total bilirubin if the total bilirubin is greater than 5 mg/dL (Moyer et al., 2004). An abnormality in these tests indicates a blockage in bile flow (Moyer et al., 2004).

To attempt to elucidate the cause of the cholestatic jaundice, the following tests were ordered: complete blood count with differential, liver function tests, blood glucose,
prothrombin time, α-1 antitrypsin, urine reducing substances, and an abdominal ultrasound (Moyer et al., 2004). In children with choledochal cysts, the pertinent lab results are as follows: elevated alkaline phosphatase, elevated serum aspartate aminotransferase, elevated serum alanine aminotransferase, and elevated gamma glutamyl transferase (see table 1) (Singhavejsakul and Ukarapol, 2008).

Among other places, alkaline phosphatase is located in the bile ducts (Toda et al., 1980). In the presence of cholestasis, the biliary alkaline phosphatase is regurgitated into the blood stream (Toda et al., 1980). This regurgitation causes the increase in serum alkaline phosphatase that is seen in patients with choledochal cysts (Toda et al., 1980).

Gamma glutamyl transferase is located, among other places, in the small bile ductule epithelium (D'Agata and Balistreri, 1999). Cholestasis causes the increase of gamma glutamyl transferase, the solubilization of gamma glutamyl transferase, and, therefore, the increase in the serum gamma glutamyl transferase level (D'Agata and Balistreri, 1999). Despite its ubiquity throughout the body, gamma glutamyl transferase elevation is limited to disease of the liver (D'Agata and Balistreri, 1999). Therefore, a rise in both alkaline phosphatase and gamma glutamyl transferase indicates cholestasis (D'Agata and Balistreri, 1999).

Aspartate aminotransferase and alanine aminotransferase are located in hepatocytes (D'Agata and Balistreri, 1999). Serum values of these enzymes increase when they are released from hepatocytes due to hepatocyte death (D'Agata and Balistreri, 1999). A choledochal cyst is not a hepatocellular disease, but the bile stasis caused by a choledochal cyst is toxic to hepatocytes, and this toxicity kills hepatocytes and leads to a
slight increase in the serum values of these enzymes in patients with choledochal cysts
(D'Agata and Balistreri, 1999).
Table 1. Example laboratory report for a 5 year old female patient with a choledochal cyst. All reference values come from Soldin et al. (Soldin et al., 2007). Prothrombin Time reference range comes from Rosenthal (Rosenthal, 1997).

<table>
<thead>
<tr>
<th>Test</th>
<th>5 Day Old Reference Values</th>
<th>Change in Patient with Choledochal Cyst</th>
<th>Example Value in Patient with Choledochal Cyst</th>
</tr>
</thead>
<tbody>
<tr>
<td>CBC</td>
<td></td>
<td>Change in Patient with Choledochal Cyst</td>
<td>Example Value in Patient with Choledochal Cyst</td>
</tr>
<tr>
<td>White Cell Count</td>
<td>5.86-16.0 x10^9/L</td>
<td>9.62 x10^9/L</td>
<td></td>
</tr>
<tr>
<td>Neutrophil Count (Absolute)</td>
<td>2.2-7.2 x10^9/L</td>
<td>5.0 x10^9/L</td>
<td></td>
</tr>
<tr>
<td>Neutrophil Count (Relative)</td>
<td>21.6-59.0%</td>
<td>52.0%</td>
<td></td>
</tr>
<tr>
<td>Lymphocyte (Absolute)</td>
<td>1.17-5.4 x10^9/L</td>
<td>4.0 x10^9/L</td>
<td></td>
</tr>
<tr>
<td>Monocyte Count (Absolute)</td>
<td>0.2-2.2 x10^9/L</td>
<td>0.5 x10^9/L</td>
<td></td>
</tr>
<tr>
<td>Monocyte Count (Relative)</td>
<td>1.3-18.7%</td>
<td>5.2%</td>
<td></td>
</tr>
<tr>
<td>Eosinophil Count (Absolute)</td>
<td>0.0-0.5 x10^9/L</td>
<td>0.1 x10^9/L</td>
<td></td>
</tr>
<tr>
<td>Eosinophil Count (Relative)</td>
<td>0-7.5%</td>
<td>1.0%</td>
<td></td>
</tr>
<tr>
<td>Basophil Count (Absolute)</td>
<td>0.02-0.07x10^9/L</td>
<td>0.02 x10^9/L</td>
<td></td>
</tr>
<tr>
<td>Basophil Count (Relative)</td>
<td>0-1%</td>
<td>0.2%</td>
<td></td>
</tr>
<tr>
<td>Platelet Count</td>
<td>95-354x10^9/L</td>
<td>244 x10^9/L</td>
<td></td>
</tr>
<tr>
<td>MPV</td>
<td>7.8-9.3fL</td>
<td>8.3fL</td>
<td></td>
</tr>
<tr>
<td>LFTs</td>
<td></td>
<td>Change in Patient with Choledochal Cyst</td>
<td>Example Value in Patient with Choledochal Cyst</td>
</tr>
<tr>
<td>ALT</td>
<td>7-54U/L</td>
<td>Mildly Elevated</td>
<td>60U/L</td>
</tr>
<tr>
<td>ALP</td>
<td>65-357U/L</td>
<td>Elevated</td>
<td>450U/L</td>
</tr>
<tr>
<td>AST</td>
<td>20-95U/L</td>
<td>Mildly Elevated</td>
<td>95U/L</td>
</tr>
<tr>
<td>γGT</td>
<td>18-148U/L</td>
<td>Elevated</td>
<td>290U/L</td>
</tr>
<tr>
<td>Total Bilirubin</td>
<td>&lt;11.7mg/dL</td>
<td>Elevated</td>
<td>15.3mg/dL</td>
</tr>
<tr>
<td>Conjugated Bilirubin</td>
<td>&lt;0.6mg/dL</td>
<td>Elevated</td>
<td>10.1mg/dL</td>
</tr>
<tr>
<td>Albumin</td>
<td>18-40g/L</td>
<td></td>
<td>22g/L</td>
</tr>
<tr>
<td>Glucose</td>
<td>47-110mg/dL</td>
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<td>89mg/dL</td>
</tr>
<tr>
<td>Prothrombin Time</td>
<td>10.1-15.3 s</td>
<td></td>
<td>10.9s</td>
</tr>
<tr>
<td>α-1 Antitrypsin</td>
<td>92-282mg/dL</td>
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<td>180mg/dL</td>
</tr>
<tr>
<td>Cholesterol</td>
<td>56-198mg/dL</td>
<td></td>
<td>163mg/dL</td>
</tr>
<tr>
<td>Urine reducing substances</td>
<td>Negative</td>
<td></td>
<td>Negative</td>
</tr>
</tbody>
</table>
Imaging Studies

Choledochal cysts are confirmed with an abdominal ultrasound (Moyer et al., 2004). This patient showed a choledochal cyst on the ultrasound. There was communication with the gall bladder, and the gall bladder was contracted (see figure 5).

Figure 5. Ultrasound of neonate with a choledochal cyst. A. Transverse cross-sectional view B. Transverse cross-sectional view inferior to A C. Transverse cross-sectional view of the junction of the cystic duct and the choledochal cyst. Image from Clifton, M.S., et al., "Prenatal diagnosis of familial type I choledochal cyst." (Pediatrics Vol. 117.3. 2006) 596-600. Print.
After confirming a diagnosis of a choledochal cyst, a Hepatobiliary Iminodiacetic Acid (HIDA) scan was performed to measure the degree of obstruction to biliary flow (Lugo-Vicente, 1995). The HIDA scan showed complete obstruction of bile flow (see figure 6).


**Treatment**

Due to the complete obstruction to bile flow, the cyst was surgically excised immediately, and a Roux-en-Y reconstruction of the biliary tract was performed (Shimotakahara et al., 2005). The patient is being followed long term using laboratory tests every year in order to detect any potential complications, including recurrence of the
cyst, stricture of the anastomosis, and cholangiocarcinoma (Shimotakahara et al., 2005; Di Sena et al., 2003).
**Discussion**

The pathogenesis of choledochal cysts is very controversial. The current research seems to signify that the presence of anomalous pancreaticobiliary duct maljunction causes the reflux of pancreatic juices into the common bile duct, which causes multiple things to happen (Babbitt, Starshak and Clemett, 1973). First, reflux of pancreatic juice causes epithelial cells to over express matrix metalloproteinase-1 and -2, which work to break down the extracellular matrix more than in a patient without a choledochal cyst (Mao, Tang and Ruan, 2008). Second, the trypsinogen in the pancreatic juices gets activated allowing activated trypsin to cleave lithostathine, which is also present in the pancreatic juices, into its insoluble form, lithostathine S1, which allows lithostathine S1 to aggregate in the common bile duct and form a protein plug that obstructs the common bile duct (Kaneko et al., 2007). This protein plug increases the pressure in the biliary tree (Kaneko et al., 2007). This increased pressure, along with a weakened duct wall caused by the matrix metalloproteinase over activity, causes the formation of a cyst in the biliary tree (Mao, Tang and Ruan, 2008).

This theory about the etiology of the disease does not take into account those cases of choledochal cysts that form in the absence of anomalous pancreaticobiliary duct maljunction. However, the definition of anomalous pancreaticobiliary duct maljunction is not agreed upon by physicians (Okada et al., 2002). For this reason, a clear definition of anomalous pancreaticobiliary duct maljunction needs to be produced because this anomaly might be present in more or less cases of choledochal cysts than is reported in the literature due to different definitions of the anomaly (Okada et al., 2002).
The current treatment of choledochal cysts is evolving from open abdomen Roux-en-Y hepaticojejunostomy to laparoscopic Roux-en-Y hepaticojejunostomy (Santore et al., 2001). Laparoscopic Roux-en-Y hepaticojejunostomy is very prevalent in Asian countries and is becoming more prevalent in the United States (Santore et al., 2001). The laparoscopic approach is generally preferred when possible because it decreases the chance for infection, decreases blood loss, and decreases the cosmetic consequences (Santore et al., 2001). Despite this, both approaches are equally successful (Santore et al., 2011).

Upon elucidation of the etiology of the disease, the treatment of choledochal cysts could become much more directed at the cause of the disease as opposed to the symptoms. Discovery of the etiology could also lead to a better understanding of the difference in presentation of choledochal cysts between age groups, and it could ultimately lead to an understanding of the curious epidemiology of the disease.

Many pediatric clinicians do not encounter patients that present with cholestatic jaundice during their time practicing because it affects approximately 0.04% of infants (Moyer et al., 2004). Because of this, cholestatic jaundice is occasionally initially diagnosed as neonatal jaundice (Moyer et al., 2004). This case study aims to elucidate the possible causes of cholestatic jaundice in infants and to bring a greater appreciation to the importance of early diagnosis of the cause of cholestatic jaundice in infants.


