Abstract

Objective: to report a case of asymptomatic cholelithiasis in a young infant and review the literature.

Methods: a case of acute asymptomatic cholelithiasis incidentally diagnosed during routine ultrasonography is described; cholelithiasis presented spontaneous resolution. Review of literature was carried out using Medline and Lilacs databases, including references of the last 45 years.

Results: a 28-week premature patient with diagnosis of cholelithiasis at 5 months of age. The patient presented the following predisposing factors: prematurity; use of total parenteral nutrition; long-term use of furosemide; and sepsis. The patient remained asymptomatic until the resolution of the condition.

Conclusion: in the literature, cholelithiasis in childhood is considered a rare condition, usually associated with hemolytic disease. The increase in the use of ultrasonography has contributed to an increase in the diagnosis among newborns and young infants. This case report alerts to the possibility of spontaneous resolution of incidentally diagnosed asymptomatic cholelithiasis.

Introduction

Cholelithiasis in infancy has been reported as a rare condition.1-4 The occurrence of cholelithiasis in the neonatal period and in young infants has been more frequently described due to the increase in use of abdominal ultrasonography.4,5 Cholelithiasis in childhood is usually associated with hemolytic disease.6 In the neonatal period, however, the following predisposing factors have been reported: prematurity; sepsis; total parenteral nutrition; long-term use of furosemide; hemolysis; and congenital anomalies of the biliary tree.1,4,7,8 Neonatal cholelithiasis may be characterized by incidental diagnosis and possible spontaneous resolution.8-11 Our objective is to report a case of asymptomatic cholelithiasis in a young infant that presented spontaneous resolution. We also intend to review the literature.

Case report

Female patient, born prematurely by C-section after gestational age of 28 weeks. Patient presented Apgar score of 7 at 1 minute and 8 at 5 minutes, and weight at birth of 750 g. Mother had history of serious preeclampsia. Infant was intubated at birth and submitted to assisted ventilation for 41 days. The patient presented hyaline membrane disease, and was given two doses of pulmonary surfactant. She also presented development of bronchopulmonary dysplasia and was given furosemide for 60 days at doses of 1-2
mg/kg/day and dexamethasone for 39 days, starting at 0.5 mg/kg/day for 3 days.

The patient presented direct hyperbilirubinemia with maximum bilirubin of 6.5 mg%, and remained in phototherapy for 6 days. Enteral feeding was initiated at 15 days of life, and the infant remained in total parenteral nutrition for 22 days. She remained with arterial and umbilical vein catheter for the first 12 days of life. The following complications were observed: sepsis; renal failure; and anemia. Nine blood transfusions were carried out; the patient was dismissed from the hospital after 93 days.

At the 5th month of chronological age, presence of gallstone was detected while abdominal ultrasonography was being carried out for investigation of nephrocalcinosis (Figure 1). Thirty days later, another ultrasonography was carried out and indicated involution of gallstone (Figure 2). The patient’s laboratory exams were normal (total bilirubin and bilirubin fraction; TGO; TGP; calcium; hematocrit), with the exception of elevated alkaline phosphatase (905 U/l - when normal, it is 150-420 U/l). At the 9th month of chronological age, 4 months after the diagnosis, another ultrasonography was carried out, and spontaneous resolution of gallstones was verified. During the 4-month follow-up period, the patient remained asymptomatic and with normal laboratory exams. Figure 3 shows an image of the empty gallbladder.

**Conclusion**

Cholelithiasis in infancy is considered rare.\(^1\)\(^-\)\(^4\) During the last 5 years, incidence of cholelithiasis in the neonatal period has been increasing due to the increase in the use of abdominal ultrasonography in this age group.\(^4\)\(^,\)\(^5\)\(^,\)\(^8\) Usually, diagnosis of cholelithiasis is incidental, observed in the investigation of other pathologies or in routine examination at neonatal Intensive Care Units.\(^8\)\(^\text{-}\)\(^10\)

Cholelithiasis in childhood is associated with hemolytic disease, congenital anomalies of the biliary tree, infection, and adolescent pregnancy.\(^3\)\(^,\)\(^6\)\(^,\)\(^12\)\(^-\)\(^15\) Neonatal cholelithiasis is rarely associated with hemolytic disease.\(^3\)\(^,\)\(^4\) The following predisposing factors have been reported in cholelithiasis in childhood: prematurity, prolonged fasting, long-term total parenteral nutrition, long-term use of furosemide, sepsis, dehydration, phototherapy, congenital anomaly of the biliary tree, Down’s syndrome, TORCH, family history, and antibiotic therapy.\(^1\)\(^,\)\(^4\)\(^,\)\(^5\)\(^,\)\(^7\)\(^,\)\(^8\)\(^,\)\(^10\)\(^,\)\(^11\)\(^,\)\(^16\)\(^-\)\(^18\) The literature also reports association of maternal predisposing factors, such as preeclampsia and diabetes, with neonatal cholelithiasis.\(^19\)
It is possible that all of the mentioned factors, associated with immaturity of enterohepatic circulation of bile acids, could determine biliary stasis - the main mechanism in formation of gallstones during the neonatal period. Other studies have indicated that neonatal cholelithiasis may be a temporary condition due to biliary stasis. The temporary characteristic of cholelithiasis could explain prenatal ultrasonography diagnosis of gallstone in fetuses with subsequent involution during intrauterine life.

Prolonged fasting and minimal enteral nutrition may yield biliary stasis, whereas a full diet stimulates bile flow and, thus, inhibits biliary stasis. Prolonged fasting also inhibits secretion of intestinal hormone, which is responsible for normal enterohepatic circulation of bile acids. The lack of hormone may alter bile composition and, consequently, lead to stasis.

In premature children, total parenteral nutrition is associated with cholestasis and formation of sludge and gallstones. Amino acids play a serious toxic role, since most enzyme pathways of its metabolism are still immature, causing accumulation of intermediary metabolites. The literature discusses the fact that total parenteral nutrition is usually associated with prolonged fasting and minimal enteral nutrition in immature newborn infants. Different authors, however, have observed that cholestasis, with consequent lithogenic disorders and formation of gallstones, is a late complication in total parenteral nutrition, especially among premature babies.

Biliary stasis favors proliferation of bacteria, and thus causes an increase in the production of beta-glucuronidase enzyme, which is a product of bacteria. This enzyme is responsible for hydrolysis of conjugated bilirubin into unconjugated bilirubin. A greater amount of unconjugated bilirubin increases saturation of the bile, causing formation of gallstones.

The use of diuretics, especially of furosemide, inhibits transportation of sodium into the cell interior, which may cause a reduction in excretion of bile acids and, consequently, the formation of gallstones. Also, furosemide may increase excretion of calcium into the bile; a mechanism which is similar to what occurs in the kidney and leads to formation of nephrocalcinosis and gallstones.

According to the literature, incidentally diagnosed asymptomatic neonatal cholelithiasis usually has a benign course, with about a 50% chance of spontaneous resolution of cases during the first 6 months of life. Resolution of cholelithiasis occurs after the dissolving of gallstone or after the fragmenting and passing of gallstone through the biliary tree. Long-term follow-up is recommended for children persisting with gallstones after 6 months of age, as long as they have remained asymptomatic. Surgical intervention should be reserved for symptomatic cases or those in which calcification of gallstone occurs. The case presented in this report is in agreement with the literature with respect to presence of the following risk factors: prematurity, sepsis, total parenteral nutrition, long-term use of furosemide, delayed introduction of enteral nutrition, use of phototherapy, and mother with history of preeclampsia. The diagnosis of our patient was incidental; it occurred during a routine follow-up ultrasonography examination of nephrocalcinosis. Formation of gallstone after the 16th week of life, however, is in opposition with the study by Randall et al., in which formation of gallstones in risk-group patients occurs primarily during the first 12 weeks of life. In our case, the patient remained asymptomatic, thus allowing observation of the case.

Table 1 was adapted from Morad et al. and presents cases of incidentally diagnosed neonatal cholelithiasis described in the literature.

In the event of incidental diagnosis of asymptomatic cholelithiasis in neonates or young infants, it is recommended to simply observe the case and carry out periodical control ultrasonographies. Usually, spontaneous resolution of gallstone occurs during the first 6 months of life. In cases of...
Table 1 - Incidental diagnosis of asymptomatic neonatal cholelithiasis; adapted from Morad et al.7

<table>
<thead>
<tr>
<th>Author</th>
<th>No. of cases</th>
<th>Sex</th>
<th>Gestational age</th>
<th>Age at diagnosis</th>
<th>Diagnosis type</th>
<th>Symptoms</th>
<th>Spontaneous resolution</th>
<th>Age at resolution</th>
<th>Additional problems</th>
</tr>
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<tr>
<td>Spence 38</td>
<td>1</td>
<td>F</td>
<td>?</td>
<td>6 hours</td>
<td>autopsy</td>
<td>no</td>
<td>no</td>
<td>–</td>
<td>intraventricular hemorrhage</td>
</tr>
<tr>
<td>Brill et al.39</td>
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<td>?</td>
<td>32 weeks</td>
<td>11 days</td>
<td>X-ray</td>
<td>chronic cholecystitis</td>
<td>no</td>
<td>3 years (resection)</td>
<td>HMD</td>
</tr>
<tr>
<td>Beretsky &amp; Lankin40</td>
<td>1</td>
<td>?</td>
<td>term</td>
<td>36 weeks (in utero)</td>
<td>US</td>
<td>no</td>
<td>yes</td>
<td>1 month</td>
<td>–</td>
</tr>
<tr>
<td>Keller et al.9</td>
<td>1</td>
<td>F</td>
<td>term</td>
<td>?</td>
<td>US</td>
<td>no</td>
<td>yes</td>
<td>2 weeks</td>
<td>vaginal mass</td>
</tr>
<tr>
<td>Jacir et al.10</td>
<td>3/1</td>
<td>M</td>
<td>term</td>
<td>3 weeks</td>
<td>US</td>
<td>no</td>
<td>yes</td>
<td>4 months</td>
<td>HPS/GER</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>F</td>
<td>term</td>
<td>2 weeks</td>
<td>US</td>
<td>no</td>
<td>yes</td>
<td>3 months</td>
<td>GER/GER</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>M</td>
<td>term</td>
<td>6 months</td>
<td>US</td>
<td>no</td>
<td>no</td>
<td>present at 2 years</td>
<td>–</td>
</tr>
<tr>
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<td>1</td>
<td>F</td>
<td>term</td>
<td>12 hours</td>
<td>US</td>
<td>no</td>
<td>yes</td>
<td>3 days</td>
<td>mesoblastic nephroma</td>
</tr>
<tr>
<td>Klingensmith 23</td>
<td>1</td>
<td>M</td>
<td>40 weeks</td>
<td>37 weeks (in utero)</td>
<td>US</td>
<td>hyperbilirubinemia</td>
<td>yes</td>
<td>43 days</td>
<td>–</td>
</tr>
<tr>
<td>Schirmer et al.14</td>
<td>9</td>
<td>F</td>
<td>term</td>
<td>7 months (in utero)</td>
<td>US</td>
<td>no</td>
<td>no</td>
<td>present at 2 years</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td></td>
<td>F</td>
<td>term</td>
<td>4 weeks</td>
<td>US</td>
<td>no</td>
<td>yes</td>
<td>6 months</td>
<td>exstrophy of the bladder</td>
</tr>
<tr>
<td></td>
<td></td>
<td>M</td>
<td>term</td>
<td>8 weeks</td>
<td>X-ray</td>
<td>chronic cholecystitis</td>
<td>no</td>
<td>–</td>
<td>hernia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>M</td>
<td>preterm</td>
<td>10 weeks</td>
<td>US</td>
<td>no</td>
<td>yes</td>
<td>1 year</td>
<td>HPS/BPD</td>
</tr>
<tr>
<td></td>
<td></td>
<td>M</td>
<td>preterm</td>
<td>4 months</td>
<td>US</td>
<td>no</td>
<td>yes</td>
<td>11 months</td>
<td>sepsis enterocolitis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>M</td>
<td>preterm</td>
<td>4 months</td>
<td>X-ray</td>
<td>no</td>
<td>no</td>
<td>present at 4 years</td>
<td>sepsis enterocolitis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>F</td>
<td>preterm</td>
<td>6 months</td>
<td>X-ray</td>
<td>no</td>
<td>no</td>
<td>present at 2 years</td>
<td>sepsis enterocolitis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>F</td>
<td>preterm</td>
<td>8 months</td>
<td>X-ray</td>
<td>chronic cholecystitis</td>
<td>no</td>
<td>–</td>
<td>sepsis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>F</td>
<td>preterm</td>
<td>10 months</td>
<td>X-ray</td>
<td>**</td>
<td>?</td>
<td>?</td>
<td>sepsis</td>
</tr>
<tr>
<td>St-Vil et al.* 4</td>
<td>5</td>
<td>?</td>
<td>2.6 months**</td>
<td>US</td>
<td>no</td>
<td>yes</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Debray et al.* 17</td>
<td>6</td>
<td>?</td>
<td>in utero up to 10 months</td>
<td>X-ray</td>
<td>no</td>
<td>yes, in 2 cases</td>
<td>–</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>Amin et al.41</td>
<td>1</td>
<td>M</td>
<td>26 weeks</td>
<td>15 weeks</td>
<td>US</td>
<td>hypertension</td>
<td>yes</td>
<td>9 months</td>
<td>HMD/BPD</td>
</tr>
<tr>
<td>Rebello et al.18</td>
<td>2</td>
<td>M</td>
<td>28 weeks</td>
<td>43 days</td>
<td>US</td>
<td>right-side mass</td>
<td>death at 68 days</td>
<td>–</td>
<td>sepsis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>M</td>
<td>28 weeks</td>
<td>64 days</td>
<td>autopsy</td>
<td>no</td>
<td>death</td>
<td>–</td>
<td>sepsis pneumothorax</td>
</tr>
<tr>
<td>Morad et al.8</td>
<td>1</td>
<td>?</td>
<td>39 weeks</td>
<td>60 hours</td>
<td>US</td>
<td>no</td>
<td>yes</td>
<td>3 months</td>
<td>no</td>
</tr>
</tbody>
</table>

HMD = Hyaline membrane disease  BPD = Bronchopulmonary dysplasia  *
HPS = Hypertrophic pyloric stenosis  US = Ultrasonography  **
GER = Gastroesophageal reflux  Authors do not describe cases separately.
* Authors do not describe age of each case; age average was calculated varying from 2 to 9 months.

Gallstones that remain unresolved after 6 months of life, the patient should be followed up for a period of up to 3 years. An aggressive approach is not warranted in cases of asymptomatic patients, since there is a 50% possibility of involution in cases of incidentally diagnosed cholelithiasis.
References