Journal of Paediatric Surgeons of Bangladesh (2019) Vol. 10 (1 & 2):1-4
Official Journal of the Association of Paediatric Surgeons of Bangladesh

Journal of Paediatric Surgeons of Bangladesh

Editorial

The risk factors of gall stone formation in children

Gall stone (Cholelithiasis) in children is relatively rare in comparison to adults. But the incidence is gradually increasing worldwide day by day. As a result both physical and financial burdens are imposing on the society. In the recent years, the worldwide prevalence of gall stone has increased from 1.9% to 4% in children[1,2]. It might be due to childhood obesity and widespread use of ultrasonogram[3,4,5]. Simultaneously, the number of performing cholecystectomy in children has increased by 213% over a 9-year period[6]. On the other hand, due to improvement of ultra sonogram techniques, cases of fetal cholelithiasis are also reported[7,8]. However, a few decades ago, gall stones in children were almost only seen in hemolytic conditions. But now a day they are increasingly observed in different non hemolytic conditions too.

The pathogenesis of gall stone formation is not fully understood yet. Gallstones are formed mainly in the gallbladder, less often in intrahepatic or extrahepatic bile ducts. Based on their composition, gallstones are classified into pigment stones, cholesterol stones, and mixed stones. Pigment stones are mainly observed in hemolytic diseases, and their incidence remains stable[6]. They are composed mainly of bilirubin and calcium salts and contain less than 20% cholesterol. Cholesterol gallstones are caused by genetic and environmental factors leading to an elevated concentration of cholesterol in the bile. They are made mostly of cholesterol (70-80%), plus calcium salts and bilirubin compounds (20-30%). Mixed gallstones composed of a mixture of the two gallstone types.

Etiologically, cholelithiasis is also divided into three groups; Hemolytic, Other known etiology, and idiopathic. 30% of all gallstones in children are due to haemolytic diseases such as sickle-cell disease, hereditary spherocytosis and thalassemia. In about 30% of cases, gallstones are due to another known etiology such as cholestasis, chronic liver disease, prolonged fasting and ileal disease or resection. In 40% of cases, gallstones are idiopathic mainly in adults and adolescent girls[6].

The pathogenesis of biliary calculi in the various inherited chronic haemolytic anaemias is not understood clearly. In haemolytic anemias, the liberated hemoglobin is broken down, and its heme component is eventually, degraded into bilirubin by the liver. Then it further conjugated in the liver and excreted in the intestine as urobilinogen which is further absorbed and excreted multiple times through the enterohepatic circulation of bile. In hemolysis the abundance of urobilinogen in the bile leads to precipitation which may become calcified, which if continuous leads to gall stone formation[9].

So far, various lithogenic gene variants have been found linked to formation of gall stones. A Swedish study showed that an inherited predisposition is responsible for 25% of the overall risk of developing gallstones[10]. Lithogenic genes 1 and 2 (*Lith1* and *Lith2*), play a role in liver cholesterol secretion and regulating bile flow, have been described in brown rat models and their human counterparts are *ABCG5* and *ABCG8* [11]. Genome-wide association study (GWAS) have found a hepatobiliary cholesterol transporter ABCG8 [p.D19H] as the most common genetic risk factor for gall stones[12]. A recent study of 214 children with cholelithiasis showed the presence of the lithogenic *ABCG8* allele p.D19H in 14.9% of children, which was much more, compared to children and adults without gallstones. Increased susceptibility to the formation of cholesterol stones is associated with

abnormal cholesterol metabolism resulting from its increased transport or lower intestinal absorption in combination with increased cholesterol synthesis[13].

The gut flora play a relevant role in human health, such as nutrition and metabolism functions, preventing the invasion of infectious agents or enhancing intestinal integrity[14]. However, infection factors may be associated with the development of cholelithiasis. Study suggests a potential connection between calcium carbonate gallbladder stones and *Clonorchis sinensis* parasite infestation[15].

There is evidence of the involvement of adipokines and hepatokines in the development of cholelithiasis in children. Higher levels of chemerin, retinol-binding protein 4 (RBP-4), and fibroblast growth factor 21 (FGF-21) have been observed in children with cholelithiasis. Taking into consideration the influence of adipose tissue in lean children, only chemerin was significantly increased in patients with cholelithiasis[16]. Based on the literature, chemerin may be both a pro-inflammatory and anti-inflammatory molecule[17].The influence of other markers of inflammation was observed by Denisova et al.[18]. In this study, increased expression of various interleukins (IL-1, IL-4, IL-6, IL-7, IL-8, and IL-17A) was observed in calculous cholecystitis.

The first study on serum lipid profile in patients with gallstone disease was recently published. The authors showed that the serum values of total cholesterol (TC), sphinganine (SPA), some ceramides differed significantly between patients with and without gallstones[19].These results suggest that serum sphingolipids may be potential biomarkers in patients with gallstone disease.

Like in adults, gall stones are also found more in girls after puberty[20]. The production of hormones in puberty, especially estrogen binds to estrogen receptors in the liver and increase the secretion of cholesterol into the bile, promoting the formation of gallstones. However, the incidence is almost equal in both genders before puberty.

Food intake has been indicated as a potential risk factor for cholelithiasis. To the best of my knowledge, no studies describing the influence of diet on the occurrence of gallstone disease in children have been published so far. However, considering the effect of diet on the incidence of cholelithiasis in adults may be of similar importance. The increased fat intake with highly refined sugars, fructose, and low fiber contents predisposes to the development of gallstones. These eating habits lead to increased biliary cholesterol concentrations and hypertriglyceridemia-induced secretion of gallbladder mucin [21]. So, it is important to provide balanced diet among children and adolescents. It seems likely that avoiding fast food and sugary drinks could help reduce the incidence of gallstone disease in children.

Total parenteral nutrition (TPN) impairs enterohepatic circulation and cholecystokinin induced gallbladder contraction resulting in biliary stasis, sludge and stone. Prolonged TPN therapy can lead to gallstones in 43% of children and it increases up to 64% in children with ileal resection or disease[22]. Sludge formation occurs more rapidly in neonates with after a mean duration of 10 days of TPN infusion, as compared to adults where it takes more than 6 weeks.

Some abnormal drug concentration in the biliary tract may promote the development of cholelithiasis. Ceftriaxone, a third generation of cephalosporin, is excreted into the biliary tract, and due to the drug interaction with calcium, it may lead to calcium-ceftriaxone precipitation.

The incidence of ceftriaxone induced pseudolithiasis is variable from 15–45%, depending on dose, duration, and predisposing host factors. Since biliary lithiasis is reversible and disappears on discontinuation of drug it has been termed pseudolithiasis. Another group at risk of cholelithiasis is patients taking long-term octreotide, a somatostatin analog, which may increase the proportion of biliary deoxycholic acid and inhibit gallbladder emptying. Gallstones or biliary deposits have been observed in nearly 33% of children with congenital hyperinsulinism during octreotide therapy.

Obesity, especially in girls has been found to increase the risk of gall stone formation[23]. It is due to impaired gallbladder motility, excessive hepatic secretion, and bile saturation of cholesterol. There is mechanical hypothesis for more prevalence of choledocholithiasis in obese children which postulates that higher body fat content in the abdominal wall causes greater intra-abdominal pressure, resulting in external pressure on the wall of the gallbladder, this relatively higher pressure in the sub-hepatic region may results in a direct stimulus which further leads to dislodgment of the stone/sludge from the gallbladder into the extrahepatic biliary tree system, causing obstruction of the bile duct. In recent past years, the mean BMI in children

with cholesterol stones was found to be higher than in children with hemolytic stones and biliary dyskinesia . On the other hand, rapid weight loss and low calorie intake may also result in formation of gall stones due to excess elimination of cholesterol through bile[24].

Gall stone disease in paediatric age group presents in a complex manner. It might be asymptomatic to life threatening pancreatitis. So, it is very important to understand the risk factors of stone formation and course of the disease to get faster diagnosis and treatment. From the above discussion, it is obvious that if not all, we can take at least some measures to prevent formation of gall stones in children. We can give full effort to prevent the child to become obese by providing healthy diet, full of fruits and vegetables and allow them to do proper exercise by outdoor games. On the other hand we can also avert from taking increased fat, highly refined sugars, fructose, and low fiber contents which are found in junk foods. Proper precautions should also be taken during the use of some medicines and TPN. Otherwise, the society will suffer more and more with such illness in near future.

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