Review paper

Hepatobiliary manifestations of inflammatory bowel disease in children

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Abstract

Inflammatory bowel disease (IBD) diagnosis and therapy is challenging for every pediatrician, especially when complicated with extraintestinal manifestations. The article reviews current literature on the hepatobiliary manifestations associated with inflammatory bowel disease in the pediatric population.

Key words: children, inflammatory bowel disease, Crohn’s disease, ulcerative colitis, hepatobiliary manifestations.

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Introduction

Although numerous studies about hepatobiliary manifestations in inflammatory bowel disease (IBD) in adults have been published, data concerning the pediatric population are still insufficient. The diagnosis of hepatic disorders often starts with abnormal liver enzyme tests, which have been found in up to 40% of pediatric patients with IBD [1-3]. The association between an increased likelihood of IBD-liver disease and elevation of alanine aminotransferase (ALT) and glutamyl transpeptidase (GGT) activities within 90 days' follow-up after the diagnosis of IBD was reported [3]. Valentino et al. estimated the probability of developing abnormal liver enzymes at 16.3% after 1 month of IBD diagnosis and even at 58% over 150 months of follow-up [4]. The 3 main groups of causes of hepatobiliary diseases in IBD patients with their supposed mechanisms related to IBD are presented in Table 1 and with reported increased risk of development are included in Table 2 [5-8]. In this review, some of them will be discussed.

Primary sclerosing cholangitis

Primary sclerosing cholangitis (PSC) is a chronic liver disease manifested by multifocal biliary strictures caused by inflammation and fibrosis. PSC’s connection with IBD is unquestionable (from 76% to around 90% of PSC patients also have IBD) and often it is diagnosed simultaneously with IBD [9-11]. The latest hypothesis of PSC development in IBD suggested that PSC is likely to have an underlying multifactorial etiology including genetic predisposition, altered gut microbiota and altered bile acid (BA) metabolism and immune-mediated processes (Table 1) [5]. Among IBD pediatric patients, the diagnosis of PSC is noted in 1.5% to 9.8% of cases, more often in ulcerative colitis (UC) [1, 4, 10, 12-14]. Deneau et al. reported PSC in 9.9% of UC children and in 0.6% of Crohn disease (CD) patients [10]. Recent reports have revealed that the prevalence of PSC in adults ranges from 0.76% to 5.4% in patients with UC and from 1.2% to 3.4% in CD patients [13-16]. IBD patients with coexistent PSC are more often men than women [11, 12]. There are differences in colonoscopy lesions in PSC-UC compared to UC patients, showing increased pancolitis, rectal sparing and backwash ileitis more commonly found in PSC-UC. Additionally, these patients more often develop colorectal carcinoma (CRC). However, in pediatric UC patients, severe liver disease may be an earlier and more common outcome than colorectal cancer [10, 15]. The data of occurrence of CRC in PSC-IBD children are not sufficient. The long-term...
study of Yoon et al. revealed that 15.4% (n = 2) of pediatric patients with PSC-IBD developed CRC in the observational period, but after 18 years of age in all cases [17]. No cholangiocarcinoma was also found in pediatric patients with IBD/PSC in this study [17]. According to American College of Gastroenterology Guidelines annual colon surveillance is recommended in every PSC adult patient with UC beginning at the time of PSC diagnosis [18]. Currently there are no guidelines for colon cancer screening in children with UC and coexisting PSC. In the pediatric population PSC remains one of the important causes of morbidity and mortality in IBD patients [10, 19]. Deneau et al. found that a child newly diagnosed with UC had approximately a 5% chance of developing PSC or autoimmune sclerosing cholangitis (ASC) and a 3% chance of liver transplantation or death due to progression to complicated liver disease over the next 5 years [10]. It is worth mentioning that PSC diagnosis may precede IBD and may develop in an IBD patient who has undergone colectomy [20-22].

Small duct phenotype of PSC is presented in patients with normal cholangiograms associated with abnormal liver biopsy result. This subunit is diagnosed in 13% of PSC cases, mainly in younger patients, and has a more favorable prognosis [9, 11].

### Autoimmune hepatitis

Autoimmune hepatitis (AIH) manifested by elevated transaminases activities, interface hepatitis in biopsy, high immunoglobulin G (IgG) concentration and
specific serum autoantibodies, coexisting with IBD has been reported. Data showed that the frequency of AIH in IBD ranged from 0.6% to 1.6%, but a population-based study conducted in Utah revealed the frequency of 0.3% [10, 12, 21, 22]. In the Gregorio et al. study involving children with autoimmune liver disease, 18% of AIH patients also manifested IBD [23]. Nowadays, the knowledge about AIH is insufficient to determine whether the AIH course differs in individuals with and without IBD and which type of AIH (1 or 2) is more prevalent in IBD [10]. However, Perdigoto et al. noted a satisfactory response to therapy in adult patients with colitis and AIH compared to patients with PSC/ASC and IBD [24]. AIH may occur in the setting of medications, mostly tumor necrosis factor α (TNF-α) inhibitors. On the other hand, in the patients most refractory to therapy with PSC/AIH combined with IBD, the effectiveness of anti-TNF-α agents has been reported [25].

### Autoimmune sclerosing cholangitis

A clear distinction between AIH and PSC in the course of IBD may be difficult because of the number of overlapping features. ASC shares the diagnostic criteria for both PSC and AIH. In the Deneau et al. study, ASC occurred in 2.3% of UC pediatric patients and 0.9% of CD children, similarly to another report by Valentino et al. (1.7% only in UC) [4, 10]. However, as many as 44% of children with ASC were also diagnosed with IBD in the Gregorio et al. study [23]. Reported data suggested that IBD patients with ASC are at greater risk of refractory disease and escalation of therapy is needed with more aggressive initial treatment [26].

### Non-alcoholic fatty liver disease

Non-alcoholic fatty liver disease (NAFLD) is characterized by excessive accumulation of fat in the liver. In adults, the estimated 8.2% prevalence of NAFLD in the IBD population is lower than 33.6% observed in the general population of the United States [27]. However, according to the systemic review of Gizard et al., the prevalence of NAFLD in IBD patients ranged from 1.5% to 56% compared to 6.3% to 33% in the general population [14]. The widespread increase of obesity among children made NAFLD a common pathology, but currently there are no available data concerning coexistence of IBD with NAFLD in the pediatric population [28]. In the Valentino et al. study ultrasound signs of fatty infiltration of the liver were detected in 18 of 129 examined children with IBD and abnormal liver enzymes, but all of them had low body mass index (BMI) [4].

### Cholelithiasis

The association between cholelithiasis and IBD has already been reported [29, 30]. In children with IBD the presence of gallstones was described in 2.3% of patients [22]. In adults, the prevalence rate of cholelithiasis was estimated from 11% to 34% of patients with CD and in UC patients, based on the systemic review, which did not significantly differ from the general population [14]. However, chronic cholecystitis is diagnosed more often in UC and CD patients compared to non-IBD ones [31]. Parente et al. suggested that increased risk of cholelithiasis in CD may be caused by ileal resection [7]. Other suggested risk factors of gallstones are parenteral nutrition, changes in bile composition and impaired gallbladder emptying after surgery (Table 1).

### Viral hepatitis

The response to HBV vaccination is significantly lower in people with IBD, as shown in the studies conducted on the IBD population of adults and children [32, 35]. It was established that only 56% of children with IBD had immunity to HBV as defined by an anti-HBs level ≥ 10 mIU/ml after the standard vaccination [34]. The absence of immunity was associated with older age, lower serum albumin levels and pancolitis. There is increased concern about reactivation of the HBV, due to chronic treatment of IBD patients with immunosuppressive drugs such as azathioprine (AZA), methotrexate (MTX) or anti-TNF-α agents, which is why the completion of vaccinations for hep-

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**Table 1. The increased risk of hepatobiliary disorders development in Crohn’s disease and ulcerative colitis**

| Hepatobiliary disorder | Crohn’s disease | Ulcerative colitis |
|------------------------|----------------|------------------|
| Primary sclerosing cholangitis | + | + |
| Autoimmune sclerosing cholangitis | + | + |
| Steatohepatitis | + | + |
| Granulomatous hepatitis | + | NA |
| Hepatic amyloidosis | + | NA |
| Liver abscess | + | NA |
| Cholelithiasis | + | NA |
| Autoimmune hepatitis | + | + |
| Primary biliary cirrhosis | NA | + |
| Drug-induced liver injury (DILI) | + | + |
| **NA** – not applicable | | |
The main manifestations of drug-induced liver diseases are presented in Table 3.

The use of methotrexate (MTX) in children with CD may be associated with elevated liver enzymes and rarely with severe fibrosis and cirrhosis when frequently applied, especially at high doses (like in adults with rheumatoid arthritis). A meta-analysis concerning prevalence of hepatotoxicity caused by MTX in pediatric IBD patients showed abnormal liver parameters in 10.2% of children, with the requirement of dose reduction in 6.4% of cases and discontinuation of therapy in 4.5% [40]. In a multicentre study, elevated liver enzymes were detected at least once in 39% of pediatric CD cases, during the first year of MTX use, and 18% required dose reduction or treatment cessation [41].

Hepatotoxicity after administration of infliximab has been reported in 0.4-6.7% of patients [42]. Among children with CD treated with infliximab, elevated alanine aminotransferase was observed in 24% of cases [43]. The mechanism is thought to be idiosyncratic. In genetically predisposed individuals, the drug reacting with cytokines may trigger the hepatic antigens and after presentation by the immune cells causes an immune reaction [44]. As mentioned above, the use of anti-TNF-α may also be associated with the risk of hepatitis B reactivation, especially when used in combination with other immunomodulatory drugs. That is why screening with serology (HBsAg, HBcAg) and vaccination for those who are seronegative is strongly recommended for all patients who might be considered for anti-TNF therapy.

Sulfasalazine can cause hepatocellular damage and cholestatic injury. It was estimated that liver toxicity affected about 0.4-2.9% of adults receiving that drug and sporadic pediatric patients [45, 46]. Newer, enteric-coated formulations, e.g. mesalamine, were reported as much safer for children [47].

Azathioprine is bio-transformed in the liver and kidneys into 6-mercaptopurine, and then into 6-thioguanine nucleotides, which have been associated with hepatotoxicity. The incidence rate of liver injury varies among studies, mainly due to lack of an opportunity for routine measurement of thiopurine metabolites. Liver injury caused by thiopurine affects about 1.4-7.1% of patients/year of the therapy and about half of the patients experience transient ALT activity elevation, which resolves spontaneously [48]. Cholestasis is rarely observed; however, it is an indication for immediate cessation of the therapy.

Corticosteroids (CCS) are recommended in the severe stage of IBD and have numerous side effects, manifested as dyslipidemia, glucose intolerance, insulin resistance, central adiposity and overt diabetes.
These medications change hepatic lipid metabolism, inducing liver steatosis. In pediatric IBD patients the duration of the CCS therapy usually does not exceed 12 weeks, but some reports suggested an association of CCS use with elevated liver enzymes [4].

**Portal vein thrombosis**

Portal vein thrombosis (PVT) is a rare complication of IBD, occurring more frequently in the setting of recent abdominal surgery [49]. PVT was found in 45% of patients undergoing restorative proctocolectomy [49]. Overall venous thromboembolism was reported in 0.7% of IBD children [50]. The proposed reasons include the mobilization of the small intestine into the mesenteric root, the tension of anastomosis of the capsule and manipulation of mesenteric vessels [49].

**Conclusions**

An increase in liver enzymes’ activity in the course of IBD always necessitates finding the cause of this condition. A diagnostic algorithm for abnormal liver enzymes in children with IBD was proposed by Valentine et al. (Fig. 1) [51]. Among hepatobiliary pathologies associated with IBD in pediatric patients, PSC and ASC are the most prevalent and important because of the potential risk of liver transplantation (LT). Abnormal liver enzymes in pediatric IBD without PSC/ASC may reflect the effect of medication hepatotoxicity or uncontrolled inflammation on the liver in IBD. Viral hepatitis screening is recommended in IBD individuals, especially for HBV due to the possible impact of immunosuppressive drugs on reactivation of the disease. Other causes of elevated liver enzymes, such as PVT, AIH and NAFLD, are rarely seen in children. Taking all these aspects into account, good cooperation between IBD clinicians, gastroenterologists and the general practitioners is needed.

**Disclosure**

The authors report no conflict of interest.

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