Long-term follow-up of children and adolescents with primary sclerosing cholangitis and autoimmune sclerosing cholangitis

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BACKGROUND: Sclerosing cholangitis (SC) is a chronic cholestatic hepatobiliary disease with uncertain long-term prognosis in pediatric patients. This study aimed to evaluate long-term results in children with SC according to the types of SC.

METHODS: We retrospectively followed up 25 children with SC over a period of 4-17 years (median 12). The diagnosis of SC was based on biochemical, histological and cholangiographic findings. Patients fulfilling diagnostic criteria for probable or definite autoimmune hepatitis at the time of diagnosis were defined as having autoimmune sclerosing cholangitis (ASC); other patients were included in a group of primary sclerosing cholangitis (PSC). The incidence of the following complications was studied: obstructive cholangitis, portal hypertension, advanced liver disease and death associated with the primary disease.

RESULTS: Fourteen (56%) patients had PSC and 11 (44%) had ASC. Patients with ASC were significantly younger at the time of diagnosis (12.3 vs 15.4 years, *P*=0.032) and had higher IgG levels (22.7 vs 17.2 g/L, *P*=0.003). The mentioned complications occurred in 4 (16%) patients with SC, exclusively in the PSC group: one patient died from colorectal cancer, one patient underwent liver transplantation and two patients, in whom severe bile duct stenosis was present at diagnosis, were endoscopically treated for acute cholangitis. Furthermore, two other children with ASC and 2 children with PSC had elevated aminotransferase levels. The 10-year overall survival was 95.8% in all patients, 100% in patients without complicated liver disease, and 75.0% in patients with complications.

CONCLUSION: In children, ASC is a frequent type of SC, whose prognosis may be better than that in patients with PSC.

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KEY WORDS: autoimmune sclerosing cholangitis; childhood; inflammatory bowel disease; primary sclerosing cholangitis; prognosis

Introduction

Primary sclerosing cholangitis (PSC) is a chronic cholestatic hepatobiliary disease characterized by inflammation with progressive obliterating fibrosis of the intrahepatic and extrahepatic bile ducts. The reported incidence of PSC in children is 0.2 per 100 000, differing from adults, in whom the incidence is 1.1 per 100 000.[1] Clinical, biochemical and immunological presentations of PSC in children and adolescents differ in many ways from symptoms seen in adult patients with this disease.[2, 3] In children and adolescents, sclerosing cholangitis (SC) often manifests as a cholestatic liver disease with significant autoimmune characteristics, i.e., autoimmune hepatitis (AIH)/SC overlap syndrome or autoimmune sclerosing cholangitis (ASC), fulfilling the criteria established by the International Autoimmune Hepatitis Group (IAIHG) for definitive or probable diagnosis of AIH.[4, 5] There is currently no effective treatment for patients with PSC, which could prevent gradual progression of liver disease to biliary cirrhosis and chronic liver failure. Liver transplantation remains the only treat-

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ment, and about 17%-21% of patients with PSC and approximately the same number of children with ASC undergo this operation in the course of the disease.[6-8] Immunosuppressive therapy is effective for ASC; however, there is no definite evidence that the long-term prognosis of patients with ASC is better than that of patients with PSC.[4] Thus, we retrospectively evaluated children with PSC and ASC, and compared their laboratory and histological results at the time of diagnosis as well as the incidence of complications during the course of follow-up and long-term prognosis.

Methods

The patients diagnosed with PSC and ASC between 1997 and 2009, who were followed up until December 2014, were retrospectively studied at the Center for Childhood Liver Disease, Department of Pediatrics of the University Hospital in Olomouc. The study was approved by the institutional ethics committee and written informed consent was obtained from parents/legal representatives of all children included in the study.

Diagnosis of SC was dependent on typical cholangiographic findings on endoscopic retrograde cholangiopancreatography (ERCP) or on magnetic resonance cholangiopancreatography (MRCP) in all patients. The extent of bile duct abnormalities was determined according to Wilschanski et al.[9] Different causes of chronic liver disease, such as hepatotropic viral infections, Wilson's disease, alpha-1-antitrypsin deficiency, cystic fibrosis, toxic liver disease including cases associated with long-term parenteral nutrition, were ruled out in all patients. Patients with PSC of small bile ducts, neonatal SC and secondary SC (resulting from injury, tumor, surgical procedure, congenital disorder or immunodeficiency) were excluded from the study. A blind liver biopsy using the Menghini needle and colonoscopy including colon biopsy were performed at the time of diagnosis in all patients whose parents provided informed consent. Histological staging of the disease was based on Ludwig's histological classification,[10] and simplified diagnostic criteria of the IAIHG for probable or definite AIH,[11] modified for pediatric age,[5] were used for ASC confirmation.

Pharmacological, invasive endoscopic and surgical treatment was evaluated in all patients. Biochemical relapse was defined by increased levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST) or gamma-glutamyltransferase (GGT) being more than two times higher than the upper reference value. Obstructive cholangitis, portal hypertension, advanced liver disease (Child-Pugh class B or C) and death associated with the primary disease were considered serious complications of SC.

Statistical analysis was performed using the software SPSS version 15.0 (SPSS Inc., Chicago, IL, USA). Fisher's exact test was used to compare categorical values. Biochemical results, age and duration of follow-up were compared using the Mann-Whitney *U* test. *P* values <0.05 were considered statistically significant. The Kaplan-Meier method was used to estimate the interval from diagnosis to the onset of complications as well as the 5- and 10-year survival rates, which were presented as point estimation of survival with standard error of survival value. Cox regression was used for univariate analysis.

Results

Clinical presentation

Of the 28 patients originally diagnosed with SC, 25 patients (14 boys and 11 girls) were included in the study (Table 1). Two patients were lost to follow-up and one patient underwent bone marrow transplantation for bone marrow aplasia, which developed 6 months after PSC diagnosis, and was not further followed up at our department. The median age at the time of diagnosis was 15 years (range 3-17); 14 years (range 3-17) in patients with ASC vs 15 years (range 12-17) in patients with PSC (*P*=0.03). The ratio of boys to girls was 5/6 in patients with ASC and 9/5 in those with PSC. The average duration of follow-up was 11.2 years (range 4-17, median 12, no significant difference between the ASC and PSC groups). The most commonly presented symptoms at the time of diagnosis, whose frequencies were also not different significantly between the two groups, were abdominal pain (36%), fatigue (24%), diarrhea (28%), weight loss or poor appetite (12%), subfebrile temperature (16%), arthralgia or myalgia (8%) and an acute onset of SC with jaundice, vomiting, and abdominal pain (16%).

Laboratory findings

According to the modified diagnostic criteria for AIH, ASC was confirmed in 11 (44%) patients, including 5 patients with probable AIH and 6 patients with definite AIH. GGT was elevated in all 25 patients whereas alkaline phosphatase (ALP) was significantly elevated only in 7 patients. There was no significant difference between the two groups regarding ALT, AST, GGT, ALP and IgM levels (Table 2). On the contrary, patients with ASC had higher IgG levels (*P*=0.003). There was no significant difference in the positivity of antineutrophil cytoplasmic antibodies (ANCA) between the two groups (11 patients with ASC, 11 with PSC, *P*=0.24), but all other antibodies were present exclusively in patients with ASC [antinuclear antibodies (ANA) in 6 patients, anti-smooth muscle antibodies (SMA) in 2, anti-soluble liver antigen antibodies