Alimentary Tract

Systematic screening for primary sclerosing cholangitis with magnetic resonance cholangiography in inflammatory bowel disease

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ABSTRACT

Background: Primary sclerosing cholangitis (PSC) is a major concern in inflammatory bowel disease (IBD).
Aims: Evaluating the use of magnetic resonance cholangiography (MRC) as a screening tool for PSC in IBD patients.
Methods: A single-center cohort study investigating systematic MRC to assess PSC in IBD patients with (cohort 1) and without (cohort 2) liver function tests (LFTs) abnormality, combined with a retrospective analysis of MRCs in a control group of non-IBD patients with abnormal LFTs (cohort 3).
Results: In total, 420 patients (cohort 1: n = 203, cohort 2: n = 30, cohort 3: n = 187) underwent imaging. MRC was classified 'abnormal' in 49/203 (24.1%) patients in cohort 1, in 1/30 (3.3%) patients in cohort 2, and in 66/187 (35.3%) patients in cohort 3 (p < 0.004 for all comparisons). PSC was diagnosed in 20/203 (9.9%) patients in cohort 1, in 1/30 (3.3%) patients in cohort 2, and in 13/187 (7.0%) patients in cohort 3 (p = 0.44). Gamma-glutamyl transpeptidase was the only independent factor predicting the diagnosis of PSC in IBD (OR 1.8, 95% CI 1.3–2.5, p = 0.001).
Conclusions: MRC revealed PSC in one tenth of IBD patients with abnormal LFTs and should be systematically performed in IBD patients with abnormal LFTs, especially if gamma-glutamyl transpeptidase level is elevated.

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1. Introduction

Primary sclerosing cholangitis (PSC) and inflammatory bowel disease (IBD) are highly linked [1]. Approximately 50–80% of PSC patients have concomitant IBD [2]. PSC is a chronic progressive disease characterized by inflammation and fibrosis of mainly medium and large bile ducts [3]. Biliary strictures may eventually lead to recurrent cholangitis, biliary cirrhosis and end-stage liver disease [4]. There is an increased risk for the development of cholangiocarcinoma in PSC [5], while surveillance strategies are limited [6]. Patients with IBD and PSC also have a higher risk of colorectal carcinoma compared to IBD patients without PSC or normal controls [7–9]. PSC is the most common liver disease specific to IBD [2]. Prevalence in ulcerative colitis (UC) and Crohn's disease (CD) has been documented from 0.8% to 5.4% and from 1.2% to 3.4%, respectively [10]. However values of alkaline phosphatase (ALP) are normal in 10% of IBD patients with PSC, liver function tests (LFTs) typically show a cholestatic profile [2,11]. Perinuclear anti-neutrophil cytoplasmic antibodies are positive in 26–94% of PSC patients but are not disease specific [6]. If cholestasis is present and secondary causes of sclerosing cholangitis (such as infection, immunodeficiency, ischemia, pancreatic disease, and immunoglobulin (Ig)G4-related conditions) are excluded, the diagnosis of PSC in IBD patients is made based on typical findings on magnetic resonance cholangiography (MRC) [2]. A liver biopsy is only warranted in patients showing biochemical and serological features of autoimmune hepatitis or if small-duct PSC, a disease variant of PSC with normal MRC, is suspected [2–4,12].

In a recent Norwegian study, the prevalence of PSC detected with MRC in patients with IBD was 8.1%, around 3-fold higher

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than that detected based on symptoms [13]. However, all examined patients had long-term (20 years) disease and only 42.6% of the original cohort underwent MRC. Furthermore, a control group of non-IBD patients was missing [13]. Therefore, whether MRC has to be performed systematically in every IBD patient, regardless of the LFTs, remains unknown.

We report our single-centre experience with the systematic use of MRC to assess PSC in IBD patients with and without abnormal LFTs. The primary aims of the study were to evaluate the prevalence of PSC and to identify factors associated with the development of PSC in a large IBD cohort. Secondary aim was to compare MRC findings in IBD patients with MRC findings in non-IBD patients that underwent MRC in the assessment of abnormal LFTs.

2. Patients and methods

2.1. Study design

We analysed MRC findings in three different cohorts of patients from our tertiary referral gastroenterology/hepatology centre (Nancy University Hospital, France). In cohort 1, MRCs were prospectively collected in IBD patients with abnormal LFTs. In cohort 2, MRCs were collected in IBD patients with normal LFTs. In cohort 3, which served as a control group, MRCs performed in non-IBD patients with abnormal LFTs were retrospectively assessed.

2.2. Data collection

2.2.1. Cohort 1: IBD patients with LFTs abnormality
Cohort 1 grouped MRC findings in IBD patients with LFT abnormality.

A complete assessment of LFTs, including alanine aminotransferase (ALT), aspartate aminotransferase (AST), ALP, gamma-glutamyl transpeptidase (GGT) and bilirubin, was prospectively performed in all IBD patients during every consecutive visit at the outpatient clinic between December 1, 2009 and February 29, 2016. LFTs abnormality was defined as an elevation of any value of ALT, AST, ALP, GGT or bilirubin above the upper limit of the normal range, and this for at least one moment of time during follow-up. Patients with LFTs abnormality systematically underwent MRC. Exclusion criteria for cohort 1 were any pre-existing known chronic biliary or liver disease, including liver cirrhosis. All patients with LFTs abnormality underwent a screening blood test, including viral serology for Hepatitis A, Hepatitis B, Hepatitis C, Human Immunodeficiency Virus, Epstein–Barr Virus, Herpes Simplex Virus and Cytomegalovirus and total gamma globulin, fasting lipid profile, glucose level, ferritin levels, total iron-binding capacity, anti-smooth muscle antibodies, anti-mitochondrial antibodies, perinuclear anti-neutrophil cytoplasmic antibodies, anti-nuclear antibodies, anti-DNA antibodies, anti-liver/kidney microsomal antibody, and anti-soluble liver antigen. A positive viral serology or detection of an alternative cause for impaired LFTs with this assessment, excluded patients from cohort 1. Lastly, drug induced liver injury was actively assessed with a thorough anamnesis, and potential harmful medication was stopped. If this led to a normalisation of LFTs, drug induced liver injury was withheld as most likely diagnosis, and this also led to exclusion from cohort 1.

LFTs that triggered MRC examination were taken into account for analysis.

2.2.2. Cohort 2: IBD patients without LFTs abnormality
Cohort 2 grouped MRC findings in IBD patients without LFT abnormality.

Following the preliminary analysis of cohort 1, we decided to initiate systematic screening of PSC with MRC in IBD patients with normal LFTs in our routine practice, to select patients for a second cohort. Nevertheless, this screening strategy was prematurely stopped following interim analysis of this group. Exclusion criteria for cohort 2 were an elevation of any value of ALT, AST, ALP, GGT or bilirubin above the upper limit of the normal range and any pre-existing known chronic biliary or liver disease, including liver cirrhosis, before MRC. All patients underwent a systematic viral and metabolic biochemistry screening, as described for cohort 1, before MRC. A positive viral serology or detection of an alternative liver disease with this assessment led to exclusion from cohort 2.

LFTs at the moment of MRC examination were taken into account for analysis.

2.2.3. Cohort 3: non-IBD patients with LFTs abnormality
Cohort 3 grouped MRC findings in non-IBD patients with LFT abnormality.

All MRCs performed in non-IBD patients in the assessment of LFTs abnormality were retrospectively assessed between May 1, 2009 and December 31, 2015. Exclusion criteria for cohort 3 were patients with any pre-existing known chronic biliary or liver disease, including liver cirrhosis and viral hepatitis.

LFTs that triggered MRC examination were taken into account for analysis.

2.3. Imaging protocol

MRCs were performed with a 3.0 T GE HDxD scanner (GE Healthcare, Waukesha, WI, USA). The protocol comprised a 2-dimensional, single-shot, fast spin-echo, short echo time sequence in the axial and coronal planes, a 2-dimensional, single-shot, free precession sequence with fat saturation in the coronal plane, a diffusion weighted sequence in the axial plane, a 3-dimensional gradient echo T1 sequence after intravenous administration of 0.2 ml/kg body weight gadoteric acid (DOTAREM, 0.5 mmol/ml; Guerbet, Villepinte, France) at a rate of 3 ml/s for a dynamic study in the axial plane (with the arterial phase 25 s after injection, the portal phase 70 s after injection, and the post-equilibrium phase 120 s after injection), and a 2-dimensional gradient echo sequence with fat saturation, at 3 min and 5 min after injection, in the axial and coronal planes. The 2-dimensional gradient echo T1 sequences, the single-shot free precession sequences and the dynamic 3-dimensional gradient echo T1 sequences after the intravenous injection of contrast medium were acquired with a breath-hold technique. All other sequences were performed applying a respiratory triggering technique. A 12-element phase-array coil was used for parallel imaging techniques, with a sensitivity-encoding factor of 2. The gradient amplitude was 33 mT/m. The whole examination lasted about 20 min.

2.4. Image analysis

The images were blindly assessed by 2 radiologists with more than 10 years of experience in abdominal MR imaging (VL, XO). Both radiologists were blinded to each other and to any clinical or biochemical data. They had no access to the initial protocol of the retrospective assessed MRCs. Disagreements were resolved by consensus reading. MRC findings were categorised as 'normal', 'PSC', 'ductopenia', 'other biliary abnormality' or 'doubt'. Criteria for PSC were multiple, typically short segment, strictures and segmental or general dilatation of the biliary tree.

2.5. Statistical analysis

Categorical variables were described by percentages and continuous variables by median and interquartile range (IQR) according to the distribution. Inter-observer reliability for detection of PSC