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Prevalence and factors associated with the presence of Abnormal Function Liver Tests in patients with ulcerative colitis

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ABSTRACT

Aim. To investigate the prevalence of abnormal function liver tests and risk factors associated with their development in Mexican patients with UC. **Methods.** A total of 200 patients with confirmed diagnosis of UC were evaluated prospectively during a one year period from January 1, 2007 to December 31, 2008. **Results.** A total of 94 females and 106 males patients with UC were analyzed. The age at diagnosis was 31.4 ± 13.2 years and the mean of disease duration was 6.7 ± 5.2 years. We found a high prevalence of abnormal function livers tests in 40% of UC patients. The pattern of abnormal function liver test was hepatitis in 70%, cholestatic (20%) and mixed (10%). The most common cause of abnormal function liver test was transient elevation in 50 patients (63%) followed by fatty liver disease (11.2%), primary sclerosing cholangitis (6.3%), drug-toxicity (6%) and others (13.5%) including chronic hepatitis C, total parenteral nutrition, granulomatous and ischemic hepatitis. In the multivariate logistic regression model, active disease, colectomy and abdominal sepsis were factors that persisted associated with the development of abnormal liver tests in UC patients. **Conclusion.** A high prevalence of abnormal function liver tests (40%) was found in Mexican UC patients is likely to be related to active disease, colectomy and the presence of sepsis.

Key words. Inflammatory bowel disease. Ulcerative colitis. Abnormal. Liver tests.

INTRODUCTION

The association of ulcerative colitis (UC) and liver disease is well recognized. It has been previously reported that inflammatory bowel disease (IBD) is frequently associated with pathologic findings in the liver and biliary tract, ranging from minor alterations, such as liver fatty changes, to severe conditions, like primary sclerosing cholangitis.[1-3]

The incidence of these complications varies in different studies depending on selection criteria and on the definition of hepatobiliary disease. The true incidence of hepatobiliary dysfunction in UC, however, can only be obtained by tests of liver function tests such as transaminases, alkaline phosphatases, and bilirubin made routinely in unselected groups of patients with UC. Because the cause of hepatic involvement in UC is enigmatic it is important to find out if the rate of this complication is increasing, because of factors unrelated to UC, or if it mirrors the incidence of UC in itself.

For instance, reported prevalences have ranged from 3% to greater than 50%, depending on whether the definition of hepatobiliary disease included only persistent elevation of hepatic biochemistries or also included transient elevation of those parameters.[4]

The aim of the present study was to investigate the prevalence of abnormal function liver tests and risk factors associated with their development in Mexican patients with UC, it is important to study such association because UC in Latin America seems to be genetically and phenotypically different to other populations.

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METHODS

Patients

Data was collected prospectively from January 1, 2007 to December 31, 2008. A total of 200 patients with confirmed diagnosis of UC were evaluated from the Inflammatory Bowel Disease Clinic at the Instituto Nacional de Ciencias Médicas y Nutrición Hospital. The diagnosis of UC was done by the presence of the following criteria: a history of diarrhea or blood in stools, macroscopic appearance by endoscopy, microscopic features on biopsy compatible with UC and no suspicion of CD on small bowel radiograph, ileo-colonoscopy, and biopsy.

Relevant clinical and demographic information in all UC patients was collected by questionnaire such as: gender, age at diagnosis, familial aggregation, smoking history, previous appendectomy, disease evolution, extension, extraintestinal manifestations, medical or surgical treatment and clinical course of disease.

The Montreal classification of disease extent of UC was used in all patients.[5] The disease activity was determined by Truelove and Witts index.[6] The clinical course of disease was defined as: Active then inactive (first episode with activity and then long-term remission for more than 5 years); intermittent activity (≥ 2 relapses in a year); chronic continual activity (persistent activity despite of medical conventional therapy) as previously described.[7]

Their past and current therapy was assessed as well as the clinical response to conventional medical therapy including 5-ASA agents, steroids and immune-modulators agents.

The prevalence of abnormal hepatic biochemistries (as defined by any elevation of serum AST, ALT, and/or ALP above the upper limit of normal) was determined by including as the numerator all patients within the study population who had abnormal liver biochemistries. The magnitude of the aminotransferases abnormalities was classified in mild (elevation of 1-3 times above upper normal value), moderate (elevation of 4-20 times above upper normal value) and severe (elevation >20 times above upper normal value or >1,000 U/L) as described previously.[8]

All patients with a persistent rise in alkaline phosphatase >5 [ukat/l (normal upper range <4-2 ukat/l) had an ultrasound investigation and subsequently also a colangio-magnetic resonance or endoscopic retrograde cholangiography. All patients with a persistent rise in transaminase activities and without a previously established hepatobiliary diagnosis were examined with conventional laboratory tests and were questioned concerning intake of alcohol or drugs, and exposure to other hepatotoxic substances. Laboratory tests included assessment of serum γ-glutamyltransferase, bilirubin, creatinine and ferritin, and serum protein electrophoresis regarding values of ceruloplasmin. Immunofluorescence analyses of smooth muscle anti-nuclear and anti-mitochondrial antibodies were made. Serological tests for hepatitis B (HBsAg, anti-HBs, and anti-HBc) and hepatitis C (anti-HCV) were done with routine techniques. All patients had ultrasonography.

Statistical analysis

Descriptive statistics are expressed as mean and standard deviation (SD). Data was analyzed by t-student test for numerical variables and chi-square and Fisher exact tests for categorical variables. When data were non-normally distributed, Wilcoxon's non parametric rank sum test was used. Those risk factors with P values <0.1 in the univariate analysis were included into the multivariate model. The results were expressed as Odds ratio (OR) with corresponding 95% confidence interval (CI). Two tailed tests for significance were used in all statistical analyses and $p < 0.05$ was considered statistically significant. The data analysis was performed with SSPS Version 15.0 for Windows.

RESULTS

Demographic and clinical characteristics

A total of 94 females and 106 males patients with UC were analyzed. The age at diagnosis was 31.4 ± 13.2 years and the mean of disease duration was 6.7 ± 5.2 years. Most of the patients were non-smokers (60%) and 80 (40 %) patients were ex-smokers. None of the patients had alcohol abuse. The extent of disease was distributed as follows: 74% had pancolitis (E3); 20% had left-sided colitis (E2); and 6% had proctitis (E1). One hundred and four UC patients (52%) had extraintestinal manifestations that included: arthropathy (42%), primary sclerosing cholangitis (6.3%), pyoderma gangrenosum (6.3%), anterior uveitis (4.0%), sacroiliitis (4%), erythema nodosum (1.3%) and ankylosing spondylitis (1.3%). Twenty-five percent showed active then inactive, 53% intermittent activity and 22% with chronic continual activity. All patients were taking sulfasalazine or 5-aminosalicylic acid (5-ASA); 67% used oral

Table 1. Demographic and clinical characteristics of UC patients.

Characteristic	Frequency
Age at diagnosis	31.4 ± 13.2 years
Female/Male	94/106
Alteration of liver enzyme	
Normal	120 patients (60%)
Abnormal	80 patients (40%)
Hepatocellular pattern	56 patients
Mild	40 patients
Moderate	16 patients
Severe	0 patients
Cholestatic pattern	16 patients
Mixed pattern	8 patients
Extent of disease	
Pancolitis	74%
Left-sided colitis	20%
Proctitis	6%
Clinical course of disease	
Active then inactive	25%
Intermitent activity	53%
Persistent activity	22%
Extraintestinal manifestations	
Present	52%
Absent	48%
Medical treatment	
5-ASA	100%
Steroids	67%
Azathioprine/6-MP	25%
Infliximab	5%

or systemic glucocorticosteroids; 25% were taking azathioprine and infliximab 5%. Topical medication was used in all patients with proctitis (6%) based on 5-ASA (Table 1). Seven percent of the UC patients were underwent total colectomy.

Prevalence of Abnormal Function Liver Tests

Abnormal function liver tests were found in 80 UC patients (40%). The pattern of abnormal function liver test was hepatocellular pattern in 56 cases (70%) distributed as follows: mild in 40 cases (71%), moderate in 16 cases (29%) and none of the patients had severe elevation of aminotransferases; cholestatic pattern in 16 cases (20%) and 8 patients with mixed pattern (10%). The cholestatic pattern was related frequently in 16 patients with primary sclerosing cholangitis and the hepatocellular and mixed patterns were inespecific. The most common cause of abnormal function liver test was transient elevation in 50 patients (63%). In all patients with occurrence of transient abnormal function tests, these enzymatic elevations were mild (<3 fold) in all cases and no etiological causes were documented including alcohol, autoimmune, hepatitis viral infection, etc. No severe cases of liver biochemical abnormalities were found in the present study.

In 30 UC patients was performed liver biopsy for persistent abnormal function liver tests. Liver biopsy specimens demonstrated the following findings: fatty liver disease (15 cases); liver drug-toxicity (7 patients); chronic hepatitis C (2 cases); autoimmune hepatitis (2 patients); small conduct primary sclerosing cholangitis (1 case); ischemic hepatitis (1 case) and two patients were associated with total parenteral nutrition. None of the patients had cirrhosis and 1 patient with chronic hepatitis had moderate fibrosis on the liver biopsy.

Radiological findings

Hepatic ultrasonography revealed normal liver morphology in most of the UC patients (150 cases) and 50 patients had evidence of fatty liver. None of the patients had indirect evidence of portal hypertension manifested by splenomegaly or thrombocytopenia. Colangio-magnetic resonance or endoscopic retrograde cholangiography was performed in 13 patients for persistent rise in alkaline phosphatase >5 fold and γ-glutamyltransferase which confirmed the presence of primary sclerosing cholangitis distributed as follows: extrahepatic in 7 cases; combined in 4 cases and intrahepatic in 2 patients.

Factors associated with Abnormal Function Liver Tests

The univariate analysis showed that clinical course characterized by intermittent activity of UC (P = 0.07); surgical procedure consisted of colectomy (P = 0.004); active disease (P = 0.0002); abdominal sepsis (P = 0.0000001) and the presence of ANA (P = 0.01) were found to be associated with the occurrence of abnormal function liver tests.

However, in the multivariate logistic regression model, active disease (P = 0.002, OR = 5.79, CI 95%: 1.94-17.79); colectomy (P = 0.004, OR = 3.65, CI 95%: 1.33-10.11) and abdominal sepsis (P =

Table 2. Factors associated with the development of abnormal function liver.

Clinical characteristics	Univariate P value	Multivariate P value	OR (CI 95%)
Active disease	0.0002	0.002	5.79 (1.94-17.79)
Abdominal sepsis	0.0000001	0.00001	4.05 (2.79-5.87)
Colectomy	0.004	0.004	3.65 (1.33-10.11)
Gender	0.491	-	-
Extent of disease	0.375	-	-
EIMs	0.218	-	-
Intermitent clinical			
Course of UC	0.071	0.115	1.85 (0.045-3.41)
C Reactive protein	0.082	0.110	1.62 (0.59-2.53)
Antinuclear antibodies	0.010	0.072	2.52 (0.94-5.67)
p-ANCA	0.207	-	-

0.00001, OR=4.05, CI 95%: 2.79-5.87) were factors independently associated with the development of abnormal liver function tests in UC patients as shown in table 2.

DISCUSSION

Our data represent the first prospective study investigating the prevalence and clinical factors associated with the development of abnormal liver function tests in UC patients from one country of Latin America. The importance to study these aspects is due to UC in Latin America seems to be genetically and phenotypically different to other populations.

In our study, we found a prevalence of 40% of abnormal function liver tests in UC patients. Several series evaluating function liver tests in these patients reported abnormal findings both in CD and in UC ranging from 3% to almost 50%.[9-17] In a multicenter study described a 12% prevalence of hepatobiliary alterations among patients with IBD.[18]

Transient abnormal values in the tests for liver function were found during periods of active total colitis in 80 of 200 UC patients. Most of these patients had pancolitis, and 54 had colectomy. In some of these patients liver function abnormalities developed during the perioperative period, but did persist for at least four weeks in those patients that had sepsis characterized by the formation of intra-abdominal abscesses after surgery.

Patients with exacerbations of UC sometimes presented with raised concentrations of serum alkaline phosphatases and transaminases. Dew, *et al.*,[19] found that 25% of the patients operated on because of inflammatory bowel disease had transient perioperative changes in liver function. Half of these patients, however, suffered from postoperative wound infections or sepsis; this was not the case in our study. Transient rises in transaminases activities can also result from total parenteral nutrition.[20] This was not, however, considered to be the cause in our patients. Hence, although the cause of the abnormal values in liver function tests during active colitis is not fully understood, liver function tests are indeed impaired but usually resolve spontaneously. Fatty change of the liver is a well known abnormality in UC and also a common finding in patients having colectomy;[21] furthermore, this change has been suggested to be related to the severity of the UC.

Liver steatosis was found in 11.2% compared to other studies that have reported higher prevalence of this condition that ranging from 13% to almost 100%.[21-22] Some studies have reported that liver steatosis is more frequent in IBD patients including UC than among healthy controls.[17,22,23] Fatty change of the liver is a well known abnormality in UC and also a common finding in patients having colectomy;[24] furthermore, this change has been suggested to be related to the severity of the colitis. In this study, fatty change was found in all patients with abnormal liver function tests and active colitis in which a liver biopsy specimen was obtained. Therefore, it may be suspected that the fatty change in this subgroup of UC patients is an unspecific manifestation of the accompanying malnutrition, anaemia, and treatment with corticosteroids.

CONCLUSION

We found a high prevalence of abnormal function liver tests associated to active disease, colectomy and abdominal sepsis.

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