Prevalence of Primary Biliary Cirrhosis–Autoimmune Hepatitis Overlap Syndrome

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BACKGROUND & AIMS: The prevalence of and the most appropriate way to diagnose the primary biliary cirrhosis (PBC)–chronic autoimmune hepatitis (AIH) overlap syndrome are uncertain. We investigated the prevalence of PBC and AIH and their level of overlap at a tertiary referral center, along with clinical, biochemical, and serologic characteristics. **METHODS:** We reviewed data from all patients with PBC (n = 609) and/or AIH (n = 15) examined at the Tufts Medical Center (Boston, MA) from January 1, 2000, to June 20, 2006. PBC was diagnosed based on 2 of the following 3 results: 6 months of positive results in tests for cholestatic liver enzymes, a positive result in a test for antimitochondrial antibodies, or a liver biopsy that indicated PBC. AIH was defined as an alanine aminotransferase level of 200 U/L or greater (≥5-fold above normal), a liver biopsy that indicated severe interface hepatitis, and levels of immunoglobulin G 2-fold or greater than that of normal. **RESULTS:** Only 6 patients with PBC (1%) met the Paris criteria for the overlap syndrome. If we included 9 patients with PBC who did not meet the Paris criteria, but had results from liver enzyme tests and liver biopsy analyses that indicated improvement after treatment with prednisone, the prevalence was 15 (2.8%). This is at the low end of previously reported prevalence values for overlap of PBC and AIH (2%–20%). **CONCLUSIONS: The prevalence of the PBC–AIH overlap syndrome varies among medical centers. We propose that if the definition of PBC–AIH overlap syndrome be modified to include patients with unequivocal responses to prednisone despite not meeting the Paris criteria, this would improve treatment of patients.**

Keywords: Liver Disease; Diagnosis; Therapy; IgG.

Primary biliary cirrhosis (PBC) and autoimmune hepatitis (AIH) are distinct autoimmune chronic liver diseases that may coexist in the same patient. The coexistence of these 2 diseases in the same patient is termed the overlap syndrome. The prevalence of the overlap syndrome in patients with PBC has ranged from 2% to 20% in case series published since 1998.[1–8] The wide variation in the prevalence of the overlap syndrome in PBC may in part be owing to the difficulty in diagnosing these 2 distinct autoimmune liver diseases in the same patient and in the lack of a uniform definition of this entity.

Currently, there is no consensus regarding the diagnosis of the PBC–AIH overlap syndrome.[1] Several criteria have been proposed. In 1998, Chazouillères et al[2] developed the Paris Criteria to diagnose the overlap syndrome. By using these criteria, Poupon et al[9] reported a 14% prevalence rate of the overlap syndrome in a cohort of 282 PBC patients seen in a Paris hepatology clinic from 1990 to 2004. These criteria recently were validated by Kuiper et al.[3] In a retrospective analysis of 134 PBC, AIH, and overlap syndrome patients followed up at a Dutch referral center for liver disease and transplantation, these investigators reported 92% sensitivity and 97% specificity when they compared the Paris criteria with their earlier clinical, histologic, and laboratory-based diagnoses.[3]

Identifying patients with overlap syndrome has important clinical and prognostic implications. Studies have shown that patients with PBC–AIH overlap syndrome usually require immunosuppressive treatment in addition to treatment with ursodeoxycholic acid (UDCA).[1] Other studies have shown increased frequency of death from liver disease and the more frequent need for liver transplantation among overlap syndrome patients when compared with PBC patients.[10]

Our objective was to define the prevalence of the overlap syndrome in a population of PBC patients seen at a tertiary referral center and to describe their clinical, biochemical, and serologic characteristics.

Methods

Patient Population and Laboratory Data

We reviewed the medical records of all PBC and AIH patients seen by one of the authors (M.M.K.) in the Gastroenterology Clinic of Tufts Medical Center from January 1, 2000, to June 20, 2006. Most patients were seen at 6-month intervals, at which time their medical histories were reviewed, patients were examined, and a complete blood count and biochemical tests of liver function were obtained. All patients had had at least 1 liver biopsy, usually at the time of diagnosis. Liver biopsies were repeated in most patients at 2- to 5-year intervals, depending on the response to medical treatment. Liver biopsies were repeated earlier (after 2 y of medical treatment) if the alkaline phosphatase level was more than twice the upper limit of normal while a patient was on adequate doses of UDCA. Pertinent patient data were extracted from the medical records and tabulated in a database. Data included the following: (1) biochemical profile; (2) serum markers of autoimmunity such as antinuclear antibody, and antimitochondrial antibody; (3) immunoglobulin G or γ-globulin levels; and (4) the medications that were used to

Abbreviations used in this paper: AIH, autoimmune hepatitis; ALT, alanine aminotransferase; AMA, antimitochondrial antibody; Ig, immunoglobulin; PBC, primary biliary cirrhosis; UDCA, ursodeoxycholic acid.

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Table 1. Patient Characteristics

Patient no.	Sex	Length of follow-up period, *mo*	Age at diagnosis, *y*	ALT level, (normal ≤ 40 U/L)	Alkaline phosphatase level (normal ≤ 130 IU)	IgG level (normal ≤ 1.3 g/dL)
1	F	61	39	219	209	1.3
2	F	126	51	251	850	1.2
3	F	34	30	171	401	0.9
4	F	219	48	248	1004	1.0
5	F	52	27	624	499	2.6
6	F	187	50	324	759	3.1
7	F	160	38	1937	251	1.7
8	F	49	39	228	977	ND
9	F	145	69	300	453	3.7
10	F	61	49	212	1294	2.3
11	F	55	65	132	315	2.6
12	M	33	62	141	231	1.8
13	F	21	48	226	909	1.1
14	F	42	27	200	906	ND
15	F	190	54	90	180	4.8
16	F	60	43	500	169	1.5
17	F	36	41	795	1267	3.4
Mean		90.1	45.9	388.1	656.6	1.67
SD		65.5	12.4	439.6	382.7	1.5

ND, not done; SD, standard deviation.

treat the underlying liver disease: ursodiol, prednisone, azathioprine, colchicine, and methotrexate.

Liver Histology

Liver biopsy specimens were interpreted by one of the authors and graded using the METAVIR scoring system.[11] The stage of fibrosis was scored as follows: 0 = no fibrosis, 1 = portal fibrosis with no septa, 2 = portal fibrosis with a few septa, 3 = portal fibrosis with numerous septa, and 4 = frank cirrhosis. The grade of activity was scored as follows: 0 = no portal inflammation, 1 = mild inflammation and liver cell necrosis, 2 = moderate inflammation and liver cell necrosis, and 3 = severe inflammation and liver cell necrosis involving portal and periportal areas and occasionally involving the parenchyma. All of the liver biopsy specimens had at least 10 portal triads.

Diagnostic Criteria

The PBC–AIH overlap syndrome was diagnosed if patients met the criteria for the diagnosis of both PBC and AIH. The diagnosis of PBC required 2 of the following 3 criteria: cholestatic liver enzyme tests present for at least 6 months, a positive antimitochondrial antibody (AMA) test, and a liver biopsy that was diagnostic of or consistent with PBC.

The diagnosis of AIH was based on the following 3 criteria: serum alanine aminotransferase (ALT) level greater than 200 IU, immunoglobulin (Ig)G levels at least twice normal, and moderate to severe interface hepatitis seen on liver biopsy. In a subsequent analysis, we included as overlap patients PBC patients who had not responded fully to UDCA alone or to UDCA plus colchicine and methotrexate but who then responded when prednisone was added. A response required normalization of liver enzyme test results and an improvement in liver histology of at least 1 U on the METAVIR activity index and no increase in the fibrosis score.

Results

A total of 609 PBC patients and 15 AIH patients were seen between January 1, 2000, and June 20, 2006. Only 6 patients (1%), all AMA positive, met all of the Paris criteria for the overlap syndrome as defined earlier (Table 1). All patients were women, and the average age at diagnosis was 50 years. The mean duration of follow-up evaluation was 85 months. All patients had both PBC and AIH at the time of diagnosis. All were treated with UDCA plus prednisone and/or azathioprine and have done well. Serum bilirubin, albumin, and prothrombin international normalized ratios have remained normal and none is a candidate for liver transplantation.

There were 6 patients, 5 women and 1 man, also 1% of our PBC population, who had an ALT level greater than 200 U/L and severe interface hepatitis but whose IgG levels were not twice normal levels. Their mean age was 47 years and the duration of the follow-up period was 79 months. Five patients had both PBC and AIH at the time of diagnosis whereas 1 patient developed AIH 14 years after she was diagnosed with PBC. Her PBC had been stable on treatment with UDCA and colchicine. After 13 years, her ALT level increased from 84 to 1937 U/L and her serum bilirubin level increased from normal to 10.7 mg/dL, whereas her alkaline phosphatase level decreased from 261 to 80 IU (which is in the normal range). A percutaneous liver biopsy showed severe interface hepatitis and scattered liver cell necrosis throughout the parenchyma. She responded to the addition of prednisone, 30 mg/d, and has been maintained on UDCA plus azathioprine. Her ALT and bilirubin levels returned to normal whereas her alkaline phosphatase level returned to its pre-AIH levels, in the 200 IU range. The other 5 patients have had stable courses on UDCA ± colchicine and prednisone and/or azathioprine. None is a candidate for liver transplantation.

One patient, a 71-year-old woman, developed steroid-responsive AIH 16 years after the onset of PBC. Her PBC had been