Position Paper

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Overlap syndromes: The International Autoimmune Hepatitis Group (IAIHG) position statement on a controversial issue

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Some patients present with overlapping features between disorders within the spectrum of autoimmune liver diseases (*i.e.* autoimmune hepatitis (AIH), primary biliary cirrhosis (PBC), and primary sclerosing cholangitis (PSC)) and are commonly classified as having an ''overlap syndrome''. Standardized definitions of ''overlap syndromes'' are lacking.

The aim of this report by the International Autoimmune Hepatitis Group (IAIHG) is to evaluate if there are important reasons to classify conditions with overlapping features between autoimmune liver diseases as separate diagnostic entities.

Definition of diagnostic criteria for overlap conditions can only be arbitrary. The IAIHG scoring system for diagnosis of AIH has been widely used to diagnose ''overlap syndromes'', but was not intended for such use and has not proven to be an efficient tool for this purpose. Some patients with overlapping features between a cholestatic and hepatitic disorder appear to benefit from treatment with a combination of ursodeoxycholic acid and immunosuppressants, but this strategy is not evidence-based, and it seems unjustified to define new diagnostic groups in this regard.

The IAIHG suggests that patients with autoimmune liver disease should be categorized according to the predominating feature(s) as AIH, PBC, and PSC/small duct PSC, respectively, and that those with overlapping features are not considered as being distinct diagnostic entities. The IAIHG scoring system should not be used to establish subgroups of patients.

Patients with PBC and PSC with features of AIH should be considered for immunosuppressive treatment. Due to the low prevalence of such ''overlap syndromes'', prospective interventional therapeutic trials cannot be expected in the foreseeable future.

Keywords: Autoimmune hepatitis; Autoimmune liver disease; Overlap syndromes; Primary biliary cirrhosis; Primary sclerosing cholangitis; Ursodeoxycholic acid.

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Abbreviations: AIH, autoimmune hepatitis; PBC, primary biliary cirrhosis; PSC, primary sclerosing cholangitis; IAIHG, International Autoimmune Hepatitis Group; ULN, upper limit of normal; ALP, alkaline phosphatase; ANA, antinuclear antibody; SMA, smooth muscle antibody; anti-LKM-1, antibodies to liver kidney microsome type 1; anti-SLA/LP, antibodies to soluble liver antigen/liver pancreas; anti-LC1, antibodies to liver cytosol antigen type 1; pANCA, perinuclear anti-neutrophil cytoplasmic antibodies; pANNA, perinuclear anti-neutrophil antibody; AMA, anti-mitochondrial antibody; PDC-E2, pyruvate dehydrogenase complex-E2; anti-gp210, antibody against nuclear pore membrane glycoprotein; anti-Sp100, antibody against nuclear protein Sp100; IBD, inflammatory bowel disease; MRC, magnetic resonance cholangiography; γGT, γ-glutamyl transpeptidase; ALT, alanine transaminase; EASL, European Association for the Study of the Liver; UDCA, ursodeoxycholic acid; ERC, endoscopic retrograde cholangiography; ASC, autoimmune sclerosing cholangitis; HLA, human leukocyte antigen; AST, aspartate transaminase; AASLD, American Association for the Study of Liver Diseases.

Introduction

Some patients within the spectrum of autoimmune liver diseases present with characteristics of both a cholestatic liver disease (*i.e.* primary biliary cirrhosis (PBC) or primary sclerosing cholangitis (PSC)) and autoimmune hepatitis (AIH). These conditions may be difficult to classify and are commonly designated as ''overlap syndromes'' [1–5]. As internationally agreed criteria defining ''overlaps'' are lacking, a variety of definitions have been applied. The terms ''AIH–PBC overlap'', ''autoimmune cholangitis'', and ''AIH–PSC overlap'' are to a large extent used as diagnostic entities, to be distinguished from ''classical'' AIH, PBC, and PSC. Due to the lack of standardization and variations in the populations under study, the characteristics of these entities vary between studies.

The International Autoimmune Hepatitis Group (IAIHG) has published three reports on criteria for the diagnosis of AIH [6–8]. The initial report provided a set of descriptive criteria and also a scoring system to be used in conjunction with the descriptive criteria for difficult cases or when a more objective assessment is required [6]. The criteria were later revised to increase the diagnostic specificity for AIH [7]. ''Overlap'' of AIH with PBC, PSC, or Wilson's disease was recognized as an interesting, albeit difficult diagnostic problem that should be addressed by an international collaboration [6,7]. Simplified diagnostic criteria for AIH

were recently published, but need to be validated [8]. In the meanwhile, the IAIHG scoring system has been widely applied to define "overlaps", although it was not actually intended for such use.

The aim of the current report by the IAIHG is to evaluate if, indeed, there are important reasons to classify conditions with overlapping features between autoimmune liver diseases as separate diagnostic syndromes, or alternatively that they should be considered variants of the "classical" diseases.

Diagnosis and heterogeneity of AIH, PBC, and PSC

AIH, PBC, and PSC all possess features that describe the archetype of patients within each disorder. On the other hand, the classical disorders are not homogeneous, and patients within each diagnosis may present with a range of clinical, biochemical, serological, and histological findings (Table 1). These variations within each disorder can make the differential diagnosis between them a challenge and lead the clinician to resort to a diagnosis of "overlap syndrome". It must be taken into account that there are limitations to the strengths, validity, and reproducibility of diagnostic tests and that disease features in the single patient can change over time and appear modified by treatment [9]. Moreover, the possibility of drug induced liver injury that can be associated with a variety of presentations, should be considered in the differential diagnosis.

AIH: diagnosis and features that may overlap with those of PBC or PSC

AIH occurs in all age groups. The patients commonly are young or middle-aged, but approximately 20% of adults with AIH present after the age of 60 years [10–12]. The majority (60–75%) of patients are female. The typical AIH patient presents with elevated serum aminotransferase levels (often 3- to 10-fold increase), marked hypergammaglobulinemia (typically IgG), positive titers of auto-antibodies, and histological findings of interface hepatitis and a portal plasma cell infiltrate [10,11]. Symptoms may be non-specific with varying severity, including fatigue, malaise, anorexia, nausea, and abdominal pain. Some patients experience jaundice and even pruritus [11,13]. Clinical findings may be normal or comprise jaundice, hepatomegaly, splenomegaly, and signs of liver cirrhosis.

An elevated serum aminotransferase activity is the predominate biochemical finding, but a variable increase in bilirubin levels and moderately elevated alkaline phosphatase (ALP) activity may also be seen [14,15]. Circulating auto-antibodies represent a hallmark of AIH and include antinuclear antibodies (ANA), smooth muscles antibodies (SMA), anti-actin antibody, antibodies against liver kidney microsome 1 (anti-LKM-1), antibodies to liver cytosol antigen type 1 (anti-LC1), antibodies to soluble liver antigen/liver pancreas (anti-SLA/LP), and perinuclear anti-neutrophil cytoplasmic antibodies (pANCA) (often atypical: perinuclear anti-neutrophil antibody (pANNA)) [11,16]. The difference in antibody patterns has led to the discrimination between two subtypes of AIH [7,10,11,15,17,18]. Significant titers ($\geqslant$1:40) of ANA and/or SMA are present in 70–80% of the patients (AIH type 1). Anti-LKM-1 is detected in 3–4% of AIH cases (AIH type 2) along with anti-LC1, but typically in the absence of ANA and SMA. Anti-SLA/LP is detected in 10–30% of cases. Anti-SLA/LP is most often found in cases of AIH-1 or AIH-2, but may also be seen among the 20–30% of AIH patients who are negative for the conventional antibodies and is then particularly useful to establish the diagnosis. The pANCA is found in 50–96% of patients with AIH-1. Approximately 10% of AIH patients do not have any of these antibodies at presentation, and therefore, their absence should not preclude the diagnosis [6,11]. Importantly, most of the antibodies may also be detected in patients with other liver diseases [10]. Even anti-SLA/LP is not entirely specific for AIH and has also been detected in cases of PBC or PSC, albeit in association with features of AIH [19–23].

A definitive diagnosis of AIH cannot be established without a liver biopsy [7,10]. However, none of the histopathological findings are specific, and in particular, interface hepatitis can be part of the disease spectrum of other hepatic disorders [6,10]. The diagnosis of AIH should not be made when definite bile duct pathology or granulomas are present [7], but some coincidental biliary injury may be observed [5,7,15,24–26]. In a review of histological bile duct abnormalities, the presence of fibrous or pleomorphic cholangitis did not distinguish patients with chronic hepatitis from patients with PBC or PSC [27]. Moreover, as many as 20 (24%) out of 84 patients who were considered classical AIH cases, had biliary changes, including destructive cholangitis in 6 (30%), ductopenia in 4 (20%), and non-destructive cholangitis in 10 (50%) [28]. These patients were anti-mitochondrial antibody (AMA) negative and did not exhibit any distinctive clinical features or treatment response. When the possibility of concurrent PBC in AIH patients with bile duct injury was later specifically addressed, it was concluded that such patients lack the features of PBC [29].

The presence of some degree of biliary involvement in AIH should therefore not necessarily lead to a change in diagnosis [10,29], but an adequate cholangiographic examination should be considered in such patients. Histological biliary changes, including bile duct damage, acute and/or chronic cholangitis, and biliary pattern of periportal hepatitis, have also been noted in 31% of children with AIH [13].

PBC: diagnosis and features that may overlap with those of AIH

The "typical" PBC patient is female in the age group 30–65 years, presenting with biochemical signs of cholestasis and the presence of AMA, being asymptomatic or suffering from fatigue or pruritus [30]. PBC is not diagnosed in children. The diagnosis can be made in patients who have elevated ALP levels of at least 6 months' duration, in combination with the presence of AMA ($\geqslant$1:40) [31,32]. A liver biopsy is not required, but may be useful to assess inflammatory activity and to stage the disease [31]. Serum aminotransferase levels usually are only slightly elevated, whereas the IgM concentration typically is increased.

AMA in high titers is present in approximately 95% of PBC patients. These AMAs are directed against acetyltransferases of the inner mitochondrial membrane; more that 90% of sera have specificity for the E2 subunit of the pyruvate dehydrogenase complex (PDC-E2). This AMA pattern is highly specific for PBC. Positive ANA titers are found in at least 1/3 of cases [31,33]. Antibodies against the nuclear pore membrane glycoprotein (anti-gp210) and against the nuclear protein Sp100 (anti-Sp100) have a high specificity (>95%) for PBC [34]. A liver biopsy is necessary for the diagnosis of PBC to be established in the absence of AMA [35]. The AMA negative PBC patients appear to have a disease