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REVIEW ARTICLE

Overlap syndromes of autoimmune hepatitis: diagnosis and treatment☆

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Abstract Some patients with autoimmune liver disease have characteristics of cholestasis, as well as of autoimmune hepatitis. Despite the fact that this is a relatively frequent clinical condition seen in referral centers for liver diseases, there is little evidence as regards the clinical management of these syndromes due to their low prevalence and the lack of standardized definitions and diagnostic criteria. This is relevant, given that published studies report that there is a lower therapeutic response and poorer outcome in patients with overlap syndrome than in those presenting solely with autoimmune hepatitis.

Whether overlap syndromes are distinct entities or the presence of 2 concurrent diseases is still a subject of debate. They should be suspected in autoimmune hepatitis patients that present with signs of cholestasis, as it is known that overlap behavior tends to be more aggressive, with higher rates of cirrhosis and the need for liver transplantation. Treatment response is also poorer and should be directed at the predominant component. Standardized definitions are necessary so that these syndromes can be studied in controlled clinical trials.

PALABRAS CLAVE
Sobreposición;
Variantes;
Hepatitis autoinmune;
Cirrosis biliar primaria;
Colangitis esclerosante primaria

Diagnóstico y tratamiento de los síndromes de sobreposición de hepatitis autoinmune

Resumen Algunos pacientes con enfermedad hepática autoinmune poseen características tanto de colestasis como de hepatitis autoinmune. A pesar de que es un escenario clínico relativamente frecuente en unidades de referencia para la atención de enfermedades hepáticas, debido a su baja prevalencia, la falta de estandarización en definiciones y en criterios diagnósticos, existe poca evidencia acerca de su manejo clínico, el cual es relevante ya que, de acuerdo a lo descrito, su respuesta terapéutica es menor y su pronóstico es peor que los de la hepatitis autoinmune aislada.

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En la actualidad, aún existe controversia acerca de si los síndromes de sobreposición son entidades diferentes o la presencia de 2 enfermedades coexistentes. Deben ser buscados en los pacientes con hepatitis autoinmune que tienen datos de colestasis ya que sabemos que su comportamiento tiende a ser más agresivo con mayores tasas de cirrosis y necesidad de trasplante hepático así como pobre respuesta al tratamiento, el cual debe ser dirigido al fenotipo principal. Hacen falta definiciones estandarizadas que permitan su estudio en ensayos clínicos controlados.

Introduction

Autoimmune liver diseases are a group of diseases characterized by an anomalous immune response directed at hepatocytes or bile ducts. Their importance lies in the fact that they can result in chronic liver damage with fibrosis and cirrhosis.[1] They are classified in relation to their clinical, biochemical, serologic, histologic, and radiologic findings.

Autoimmune liver diseases are divided into 2 groups; the first is characterized by predominantly hepatocellular damage and its prototype is autoimmune hepatitis (AIH). The second is characterized by cholestasis and includes primary biliary cirrhosis (PBC) and primary sclerosing cholangitis (PSC).[2–4]

These diseases have been identified as clinical syndromes with their own diagnostic criteria and classic phenotypical presentations. However, there is no etiologic agent or characteristic pathogenic pathway whose measurement would enable us to make an accurate diagnosis.[5] Evidence indicates that AIH, PBC, and PSC share pathophysiologic mechanisms. Even though these mechanisms are not yet fully understood, it is known that they are based on the interaction between genetic predisposition and triggering environmental factors that, associated with immunologic self-regulation defects, cause immunotolerance disruption and induce tissue damage mediated by antibodies and T-cells.[6–8] In AIH, histologic damage is observed predominantly in the portal and periportal hepatocytes, whereas in PBC and PSC the histologic lesion affects the biliary epithelial cells, each with its distinctive characteristics.[9]

Overlap syndromes encompass a small group of patients within the spectrum of the autoimmune liver diseases that can have the characteristics of cholestasis (PBC or PSC) in combination with AIH.[10] In overlap syndromes the characteristics of the coexisting diseases may present simultaneously or consecutively, resulting in the ongoing debate as to whether these syndromes should be considered distinct entities or variants of the primary diseases.[11] Overlap syndromes apparently affect young AIH patients more frequently and their symptoms, which are very nonspecific, include fatigue, arthralgia, and pruritus.[12]

Due to the heterogeneous presentation of the overlap syndromes, the absence of standardized definitions and criteria, and the lack of controlled clinical trials, their treatment is largely empirical and extrapolated from the primary diseases.

Types and diagnoses of overlap syndromes

Each one of the autoimmune liver diseases has specific classic characteristics (table 1). Nevertheless, they are not completely homogeneous, and in relation to each disease, patients can present with a spectrum of different clinical, biochemical, serologic, and radiologic characteristics. Furthermore, the variability in the validation and reproducibility of the criteria and diagnostic tests must be taken into account, adding to the complexity of their classification and differential diagnoses.[12]

Approximately 18% of the patients with autoimmune hepatopathy present with characteristics that are distinctive of a second autoimmune hepatic disease. The term overlap syndrome refers to the coexistence of 2 autoimmune diseases in the same patient.[10,13] Thus, AIH can present with 3 cholestatic phenotypes that can be intermixed with its classic ''hepatic'' characteristics[8] (table 2).

In relation to clinical practice, the presence of an overlap syndrome should be suspected when, in the setting of an autoimmune hepatopathy, there is a deviation in its natural progression, the biochemical and serologic patterns are not classic, or the therapeutic response is not the expected one.[14]

The nomenclature of the overlap syndromes has transformed over time. Specific terms used to be employed to define some of them (e.g. autoimmune sclerosing cholangitis for AIH/PSC overlap in children or autoimmune cholangitis for the AIH/undetermined cholestasis overlap). However, in order to avoid confusion and homogenize their classification, it is recommended to first name the dominant phenotype and then the secondary phenotype (e.g. AIH/PBC or AIH/PSC).

Unlike autoimmune liver diseases as isolated entities, overlap syndromes lack specific diagnostic criteria. Therefore, proposals to that end have been made that will be discussed further ahead. It is also recommended to define each of the primary autoimmune hepatopathies in accordance with the criteria that has been validated by the different international groups and associations, such as the International Autoimmune Hepatitis Group (IAIHG), the American Association for the Study of Liver Diseases (AASLD), and the European Association for the Study of the Liver (EASL).[15]