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REVIEW

Autoimmune hepatitis: From mechanisms to therapy

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Abstract Autoimmune hepatitis (AIH) is a progressive inflammatory hepatopathy and an important cause of end-stage liver disease. Its aetiology remains unknown, though both genetic and environmental factors are involved in its development. The major mechanism of autoimmune liver damage involves immune reactions against host liver antigens. Numerical and functional defects of regulatory T-cells play a permissive role enabling autoimmune liver injury to occur and persist. The most typical features of AIH are female preponderance, hypergammaglobulinaemia, seropositivity for circulating autoantibodies and a picture of interface hepatitis on histology. Two types of AIH are distinguished according to serological profile: AIH type 1 patients are positive for anti-nuclear and/or anti-smooth muscle antibodies, whereas AIH type 2 patients are defined by the positivity for anti-liver kidney microsomal type 1 antibody and/or for anti-liver cytosol type 1 antibody. Clinical manifestations are variable, and AIH onset is often ill-defined, frequently mimicking acute hepatitis; its course may be fluctuating. AIH responds to immunosuppressive treatment in the majority of cases. Steroids with or without azathioprine should be instituted promptly upon diagnosis. Remission is achieved in some 80% of patients. For the remaining 20% of patients, alternative immunosuppressive agents such as mycophenolate mofetil and calcineurin inhibitors are an option. Liver transplantation should be considered for those patients who progress to cirrhosis and develop complications of end-stage liver disease, as well as for those presenting with acute liver failure; outcomes are excellent, although the disease may recur in the allograft.

PALABRAS CLAVE
Hepatitis autoinmune;
Patogenia;

La hepatitis autoinmune: de los mecanismos al tratamiento

Resumen La hepatitis autoinmune (HAI) es una hepatopatía inflamatoria progresiva y una causa importante de insuficiencia hepática terminal. Su origen continúa siendo una incógnita, si bien influyen en su evolución factores tanto genéticos como ambientales. El principal

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mecanismo de daño hepático autoinmune son las reacciones inmunitarias contra los antígenos hepáticos del receptor. Los defectos numéricos y funcionales de los linfocitos T reguladores desempeñan un permisivo papel a la hora de propiciar que la enfermedad hepática autoinmune se produzca y perdure. Las particularidades más típicas de la HAI son el predominio femenino, hipergammaglobulinemia, seropositividad para autoanticuerpos circulantes e imagen de hepatitis de interfase en la histología. Se distinguen 2 tipos de HAI conforme a su perfil serológico: los pacientes con HAI tipo 1 dan positivo para anticuerpos antinucleares y/o antimúsculo liso, mientras que los pacientes con HAI tipo 2 dan positivo para el anticuerpo antimicrosomal de hígado tipo 1 y/o para el anticuerpo contra el citosol hepático 1. Los signos clínicos varían, y el inicio de la HAI suele estar mal definido, imitando hepatitis aguda; su evolución puede fluctuar. La HAI remite con tratamiento inmunodepresor en la mayoría de los casos. Los corticosteroides con o sin azatioprina deberían iniciarse inmediatamente después del diagnóstico. La remisión se consigue en alrededor del 80% de los pacientes. Para el 20% restante, una opción son los fármacos inmunodepresores, como el micofenolato de mofetilo o inhibidores de calcineurina. El trasplante hepático debe ser tenido en cuenta para aquellos pacientes que cursen con cirrosis y padezcan complicaciones de insuficiencia hepática terminal, así como para los que experimenten insuficiencia hepática aguda; los resultados son excelentes, si bien la enfermedad podría recidivar en el alotransplante.

Introduction

Autoimmune hepatitis (AIH) is an immune-mediated inflammatory liver disease characterised serologically by hypergammaglobulinaemia and the presence of non-organ and liver-specific autoantibodies, and histologically by a dense mononuclear cell infiltrate in the portal tract.[1] Two types of AIH are recognised: AIH type 1 (AIH-1), defined by the presence of anti-smooth muscle (SMA) and/or anti-nuclear (ANA) antibodies; and AIH type 2 (AIH-2), defined by positivity for anti-liver kidney microsomal type 1 (anti-LKM-1) and/or anti-liver cytosol type 1 (anti-LC-1) antibodies.[2,3]

AIH occurs globally, affecting children and adults of all ages and both sexes, although it is more commonly found in females.[4] There are no robust epidemiological data on AIH. Available studies show an incidence of 1.5–2.0 cases per 100,000 people per year in Northern Europe.[5,6] Prevalence estimates range from 16.9 cases per 100,000 people in Northern Europe to 35.9 cases per 100,000 people in Alaskan natives.[5,7] While AIH-1 affects both children and adults, AIH-2 is mainly a paediatric condition.[8] Female predominance is a feature of both types.[8]

The mechanisms responsible for its development include genetic predisposition to autoimmunity through possession of specific human leucocyte antigen (HLA) alleles, immune reactions to liver cell antigens, possibly triggered by a mechanism of molecular mimicry, and impairment in immune regulation.[9]

AIH has variable modes of presentation: it can present insidiously, with complications of portal hypertension, or with a clinical picture of acute hepatitis, or more rarely with acute liver failure (ALF).[4,10] In addition, variant forms of the disease, presenting with concomitant features of primary biliary cholangitis (PBC) or primary sclerosing cholangitis (PSC) are increasingly recognised.[11] AIH should be considered during the diagnostic workup of any increase in liver enzyme levels.[12] A set of inclusion and exclusion criteria for the diagnosis of AIH have been established, and meanwhile revised, by the International Autoimmune Hepatitis Group (IAIHG).[13,14] Immunosuppressive therapy with steroids, with or without azathioprine, remains the mainstay of treatment, and should be instituted as soon as the diagnosis is made.[1] Difficult-to-treat or non-responsive patients should be treated with mycophenolate mofetil (MMF) or calcineurin inhibitors (CNI).[1,4] Persistent failure to respond or lack of adherence to treatment result in end-stage liver disease. Patients with end-stage liver disease, and those with ALF at diagnosis, will require liver transplantation (LT).[15]

This review aims to discuss the recent advances in the understanding of AIH pathogenesis, diagnosis, and treatment.

Genetics

AIH is a ''complex trait'' disease that does not follow a Mendelian pattern of inheritance. The mode of inheritance of a complex trait disorder is unknown, though it involves one or more genes, operating alone or in concert, to increase or reduce the risk of the trait and interacting with environmental factors.

Predisposition to AIH is linked to Major Histocompatibility Complex (MHC) class II genes, more specifically to the Human Leucocyte Antigen (HLA)-DR locus, located on the short arm of chromosome 6 – which are involved in the presentation of antigenic peptides to T-cells, and are therefore implicated in the initiation of an adaptive immune response.[16,17] In Europe and North America, the alleles conferring susceptibility to AIH-1 are *DRB1*0301* and *DRB1*0401*, which encode the HLA DR3 and DR4 antigens, respectively.[18] The first genome wide association study (GWAS) in AIH performed in Dutch AIH-1 patients and replicated in a cohort of

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