Journal of Autoimmunity 75 (2016) 6–19

Contents lists available at ScienceDirect

Journal of Autoimmunity

journal homepage: www.elsevier.com/locate/jautimm

Review article

Cutting edge issues in autoimmune hepatitis

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ARTICLE INFO

Article history:
Received 28 April 2016
Received in revised form
6 July 2016
Accepted 10 July 2016
Available online 5 August 2016

Keywords:
Autoimmune hepatitis
Pathogenesis
Immunosuppression
International Autoimmune Hepatitis Group

ABSTRACT

Autoimmune hepatitis (AIH) is a severe liver disease affecting all age groups worldwide. Novel basic and clinical aspects of AIH, addressed at a Monothematic Conference in London in September 2015, are highlighted in this review. The diagnosis of AIH relies upon detection of characteristic autoantibodies, hypergammaglobulinemia, and interface hepatitis on liver histology. The International Autoimmune Hepatitis Group (IAIHG) has devised diagnostic scoring systems to help in comparative studies and clinical practice. AIH arises in a genetically predisposed host, when yet unknown triggers – such an encounter with a pathogen – lead to a T cell-mediated immune response targeting liver autoantigens. This immune response is inadequately controlled because regulatory mechanisms are impaired. The mainstay of treatment for AIH is immunosuppression, which should be instituted as soon as the diagnosis is made. Standard treatment regimens include relatively high doses of predniso(lo)ne, which are tapered gradually as azathioprine is introduced. Recent guidelines have described newer treatment regimens and have tightened the goal of therapy to complete normalization of biochemical, serological and histological parameters. Mycophenolate mofetil, calcineurin inhibitors, mTOR inhibitors and biological agents are potential salvage therapies, but should be reserved for selected non-responsive patients and administered only in experienced centers. Liver transplantation is a life-saving option for those patients who progress to end-stage liver disease. Further dissection of cellular and molecular pathways involved in AIH pathogenesis is likely to lead to the discovery of novel, tailored and better tolerated therapies.

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http://dx.doi.org/10.1016/j.jaut.2016.07.005
0896-8411/

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1. Introduction

In 1965, about a decade after the concept of immune tolerance had been established, Ian Mackay and colleagues proposed the term autoimmune hepatitis, now widely accepted by the hepatology community, for a form of chronic liver disease characterized by hyperglobulinemia and a mixed histological infiltrate of plasma cells and lymphocytes that had been recognized already in the 1950s by Jan Gösta Waldenström [1,2]. The presence of lupus erythematosus cells and the detection of anti-nuclear antibody (ANA) seropositivity, previously had led to the adoption of the term "lupoid hepatitis" and the idea that the condition stemmed from a loss of immunological tolerance [3]. The positive impact of glucocorticosteroid therapy, initially recognized in the 1950s, resulted in the publication of three controlled clinical trials which incontrovertibly showed the life-saving value of corticosteroids [4–6]. The recognition that "chronic active autoimmune hepatitis", as it was then known, constituted a distinct clinical entity, led to the systematic evaluation of its clinical symptoms, laboratory features, and molecular immunopathology [7]. During two working meetings held in the early 1990s, the International Autoimmune Hepatitis Group (IAIHG) formally endorsed the term autoimmune hepatitis, as originally suggested in 1965 [8], as the most appropriate and least redundant name, noting that the disease frequently presents acutely, often has a fluctuating course, characterized by spontaneous remission, and periods of inactivity [9,10]. The IAIHG continues to monitor developments in the field and was responsible for devising an AIH scoring system, which was subsequently revised [9,10]. More recently, a simplified system, designed for use in individual patients in clinical practice, was proposed which has gained wide acceptance [11].

Two types of AIH are recognized, based on the serological autoantibody profile: AIH type 1 (AIH-1) is defined by positivity for ANA and/or anti-smooth muscle antibody (SMA), whereas AIH type 2 (AIH-2) is characterized by the presence of anti-liver kidney microsomal type 1 antibody (anti-LKM-1) or anti-liver cytosol type 1 antibody (anti-LC-1). Besides the presence of autoantibodies, AIH is associated with elevated transaminase and immunoglobulin G (IgG) levels, and histologically, with interface hepatitis. In symptomatic cases, immunosuppressive therapy, which remains the mainstay of treatment, should be instituted as soon as the diagnosis is made to avoid progression of disease and, generally, the response is good. If left untreated, AIH usually progresses to liver failure requiring transplantation [12,13]. The etiology of AIH is unknown, though both genetic and environmental factors are likely to be involved. An immune response targeting liver autoantigens, unrestrained because of the failure of immunoregulatory mechanisms, is thought to initiate and perpetuate the liver damage [14].

Sixteen years after the American Association for the Study of the Liver (AASLD) convened a Single Topic Conference on clinical aspects of AIH, Atlanta 1999 [15], a Monothematic Conference dedicated to AIH took place in London in September 2015. This 2-day conference, jointly sponsored by the European Association for the Study of the Liver (EASL) and the AASLD, covered both pathogenic and clinical aspects of the disease. This review summarizes the topics discussed, highlighting recent breakthroughs in our understanding of the pathogenesis of AIH and linking them to advances in clinical practice.

2. Epidemiology

AIH most commonly affects females, with a male:female ratio of 1:4 [16]. Although the peak incidences of the disease are in adolescence and at 30–45 years of age, AIH can affect children and adults of all ages [16]. The exact incidence and prevalence of AIH are unknown because most studies were conducted before the introduction of standardized criteria developed by the IAIHG [9]. Reported prevalences varies from 11.6 cases per 100,000 inhabitants over the age of 14 in Spain [17], to 24.5 per 100.000 in New Zealand and 35.9 cases per 100,000 in Alaskan natives [18,19]. Reported mean annual incidences are 1.9 cases per 100,000 inhabitants in the Norwegian population [20], and 3 cases per 100,000 inhabitants in the United Kingdom [21]. More recently, a nationwide registry-based cohort study from Denmark reported an incidence rate of 1.68 cases per 100,000 people and demonstrated that the incidence of the disease increased during 1994–2012 [22]. A recent study including all pediatric centres in Canada and using the IAIHG standardized criteria reported an annual incidence of AIH of 0.23 cases per 100,000 children [23]. AIH is thought to be less frequent in Asia; in Japan the incidence and prevalence are estimated to be 1.5 and 15.0 cases per 100,000 people respectively [24]. Epidemiological studies are detailed in Table 1.

3. Pathogenesis

3.1. Genetics

AIH is a 'complex trait' disease: at variance with single gene disorders, where a single mutation is responsible for a complete phenotype, the inheritance of AIH involves both genetic and environmental factors whose interaction either increase or reduce the risk of the disease [25]. Susceptibility to AIH is strongly influenced