Clinical Aspects of Liver Diseases

33 Autoimmune hepatitis

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► A particular form of chronic liver disease prevalent among young women with an excessive increase in protein and γ-globulin was first described by S. Amberg (1942) (1) and later by J. Waldenström (1950), who used the name **"autoimmune hepatitis"**. (101). In 1951 H.G. Kunkel et al. termed this condition **"hypergammaglobulinaemic chronic hepatitis"**. (47) This type of disease was confirmed by A.G. Bearn et al. (1956) (2) and, because of a positive LE-cell phenomenon in about 10% of cases (R.A. Joske et al., 1955) (43), was given the name **"lupoid hepatitis"** by I.R. MacKay et al. (1956). (49) • During the following years, there were frequent reports of a particular form of active and necrotizing liver disease, which was assumed in many cases to be autoimmune due to the treatment success achieved with glucocorticoids and/or azathioprine. Laboratory parameters were characterized by increased transaminase values, GDH, γ-globulins and immunoglobulins as well as by distinct histological findings – *there was no possibility of obtaining immunologic evidence at that time.*

1 Definition

The cause of autoimmune hepatitis (AIH) is unknown. Autoimmune reactions lead to a chronic (rarely acute) inflammatory process (periportal piecemeal necrosis, infiltration of portal zones). AIH is frequently associated with autoimmune diseases of other organs. It occurs predominantly among women, particularly in younger years. Hypergammaglobulinaemia is invariably in evidence. Various autoantibodies to components of the liver parenchyma are found. The presence and specificity of these antibodies, together with the respective clinical symptoms, facilitate differentiation between the various subtypes of AIH. Diagnosis is substantiated by the response to immunosuppressive therapy. If left untreated, AIH progresses rapidly with transition to cirrhosis and/or liver failure. If treated adequately, the course taken by the disease is favourable.

2 Epidemiology

AIH is present worldwide. Some 15–20% of all patients with chronic hepatitis can be classified as AIH. Prevalence and incidence differ in various geographic regions. In Europe and North America, *prevalence* ranges between 3–17/100,000 inhabitants, whereby the lowest rates are found in southern countries. The *incidence* in Europe and North America is estimated to be between 0.1–1.9/100,000 inhabitants per year. Women are 4 to 5 times and children 7 to 9 times more frequently affected. AIH can occur in all age groups. (7)

3 Aetiology

3.1 Immunologic tolerance

The aetiology of autoimmune hepatitis is (as yet) unresolved. • The immunologic tolerance of the body's own cell structures can be disturbed as a result of (*1.*) immunogenetic abnormalities in the **MHC system** (= major histocompatibility complex, i.e. the main complex in the HLA system, classes I and II), (*2.*) **clonal deletion** (= removal of so-called "mobile" genes from plasmids) as well as suppressor defects, and (*3.*) **molecular mimicry** (= partial correspondence of the molecular structure of a foreign antigen with a certain body-own protein structure). (s. p. 643)

3.2 Immunogenetic susceptibility

Genetic predisposition is paramount. • The existence of such a genetic factor can be deduced from occasional familial occurrence (25, 37), gender and age specificity as well as a close correlation with the HLA system. (64) Women are affected in 85–90% of cases, mainly between the ages of 14–55 years (women: men = 4:1).

3.3 Trigger factors

AIH must be triggered by an antigen. • Trigger factors include environmental noxae, medication, toxins, bacteria (e.g. salmonella antigen), hepatitis viruses HAV (72, 89, 95), HBV, HCV, Epstein-Barr (63, 96), lymphochoriomeningitis virus (39) and measles viruses (77, 97) as well as the Herpes simplex virus (type 1 of which is mainly responsible for AIH type 2). (48, 74) The development of AIH has also been precipitated by interferon therapy in chronic hepatitis B (13) and C (32, 66) even in children. (78) • The *viral trigger hypothesis* has recently aroused great interest, since various viruses (e.g. HAV, measles, Epstein-Barr) are known to persist "unnoticed" for years, e.g. in lymphocytes.

4 Pathogenesis

4.1 HLA system

Immunogenetic susceptibility is substantiated by the close association between autoimmune hepatitis and the HLA system. (24, 50, 64, 81) **Ethnic differences are evident:** an association with HLA-DR4 is frequent in Japan and in the Euro-Caucasian population. In patients with HLA-DR3 positivity, manifestation occurs in younger years, there is greater activity of disease and the outcome of therapy is less favourable (higher rate of non-responders and recurrences after ceasing immunosuppressive therapy, as well as more frequent indications for liver transplantation). In contrast, HLA-DR4 positivity correlates with manifestation at a more advanced age, a milder course of disease and a good response to immunosuppressives, albeit with the considerably more frequent occurrence of extrahepatic syndromes. The HLA markers DR3 and DR4 are hence characteristic of two different courses. • Further HLA types of importance include: HLA-A1, -B8, -DR4, -Bw54, -DR3, -DR13 (Brazil), -Dw3, -DR53, -C4AQO and -DQ4. A close relationship was found between AIH and the CD 45 gene, which is considered quasi to be a *"modifier gene of human autoimmunity"*. (99)