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**Autoimmune hepatitis as a rare cause of cirrhosis development**

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**Abstract**

Cirrhosis is a serious condition associated with progressive damage to this organ. Autoimmune hepatitis (AIH) is one of the causes leading to the development of cirrhosis. This disease is characterized by chronic inflammation with damage to hepatocytes and presence of specific immune markers. The diagnosis of AIH is based on biochemical, immunoserological and histopathological tests. There are defined diagnostic criteria, liver biopsy is important in determining the extent of the disease. Symptoms of AIH are nonspecific and include weight loss, fatigue, jaundice, abdominal pain and symptoms associated with the overactivity of an immune system. Advanced cases of AIH can lead to cirrhosis. AIH most often affects middle-aged women, although it can occur in people of any age. Epidemiological data indicate an increase in the incidence of AIH, which may be related to various environmental factors. The rate of progression of AIH to cirrhosis and depends on a number of factors. Effective treatment includes immunosuppression, mainly the use of glucocorticosteroids and azathioprine. Monitoring, healthy lifestyle and patient education are key. In severe cases, liver transplantation may be necessary.

**Keywords:** autoimmune hepatitis, cirrhosis, AIH

**Introduction**

Cirrhosis is a serious disease characterized by progressive liver damage and loss of liver function. It is the final stage of many chronic liver diseases. One of the factors leading to cirrhosis may be autoimmune hepatitis (AIH) [1]. Autoimmune hepatitis (AIH) is a progressive chronic disease whose manifestation is characterized by necroinflammatory lesions that cause damage to hepatocytes [2]. In this disease, there is a high increase in alanine amylase (ALT), aspartate aminotransferase (AST), an increase in immunoglobulin G (IgG) and the presence of typical antibodies [3]. By detecting the relevant antibodies, we can divide AIH into two subtypes. Type I autoimmune hepatitis, for which antinuclear antibodies (ANA) and/or smooth muscle antibodies (SMA) are characteristic. For type II autoimmune hepatitis, type 1 anti-hepatic/kidney-microsomal antibodies (anti-LKM-1) or type 1 anti-cytosolic antibodies (anti-LC1) are typical [4].

**Pathogenesis**

The pathogenesis of autoimmune hepatitis is not known in detail, but we can speculate that genetic predisposition, an imbalance between effector and regulatory immunity, and molecular mimicry are key to the development of the disease. [5] In the European population, a correlation between the incidence of AIH and HLA-DRB1\*0301 and HLA-DRB1\*0401 has been demonstrated [6].

Possible causes for the development of the disease are thought to be malfunction and deficiency of regulatory T lymphocytes (T-reg). T-reg lymphocytes regulate the presentation of autoantigens to CD4pos T lymphocytes (Th0), with a deficiency or malfunction of T-reg lymphocytes, the presentation of autoantigens is excessive, resulting in adverse events. Increased activation of Th0 cells results in the differentiation of these cells into Th1, Th2 or Th17 lymphocytes, which trigger a cascade of immune responses by the cytokines they produce [2,4].

Certain drugs are also agents that can induce AIH, among which nitrofurantoin, infliximab, minocycline are the most commonly mentioned. Metabolites of these drugs formed in the liver are recognized as foreign, and the immune system reacts inappropriately to them [7].

**Epidemiology**

AIH can develop in a person of any age, but it most commonly affects middle-aged women, regardless of ethnic group [3,8]. In 2016, a comparative analysis of 2004 studies of AHI patients in Japan was conducted. The study included 30,330 (95% confidence interval [CI] 29,592-31,069) of which the point prevalence of AIH per 100,000 population was 23.9 (95% CI, 23.3-24.5). Comparing these data with 2004 where the point prevalence of AHI was 8.7, we have an almost threefold increase in the prevalence of AHI [8]. The prevalence of autoimmune hepatitis is on the rise, as confirmed by a study in Denmark, comparing data from 1994 and 2014 showed an increase of 1.37 in 1994 to 2.33 in 2014 [10].

**Clinical picture**

The symptoms that AIH patients present with are not specific and can be a symptom of many other conditions. They can be very mild and atypical, making it difficult to make a correct diagnosis. The symptoms a patient may present with can be divided into:

*General symptoms:*

* Patients with AIH may experience general symptoms such as weight loss, fatigue, weakness, and sometimes there is an elevated body temperature.

*Liver-related symptoms:*

* As the disease progresses, patients may experience symptoms related to liver damage, such as jaundice (yellowing of the skin and mucous membranes), pruritic skin, dark colored urine and light stools.
* Hepatomegaly (liver enlargement), which we can feel on physical examination [11].

*Abdominal pain:*

* Patients may experience abdominal pain, especially in the right subcostal region.

*Autoimmune symptoms:*

* AIH is often accompanied by symptoms related to an overreactive immune system. These may include skin lesions, arthritis, vascular lesions such as telangiectasias (dilated blood vessels) or symptoms of oral mucositis.

*Symptoms of portal hypertension:*

* In advanced cases, AIH can lead to portal hypertension, which in turn manifests as esophageal and gastric varices, enlargement of the spleen, and ascites.

*Neuropsychiatric symptoms:*

* Rarely, but in severe cases, AIH can cause neuropsychiatric symptoms such as hepatic encephalopathy, which manifests as impaired consciousness, mood changes or sleep disturbances.

*Progressive liver damage:*

* If AIH is left untreated, it can lead to progressive liver damage, eventually leading to
* the development of cirrhosis [2,12].

**Diagnosis**

The diagnosis of autoimmune hepatitis is based on 3 main aspects: biochemical tests, immunoserological tests and histopathological evaluation of the material collected during liver biopsy. An important aspect is the exclusion of other liver pathologies that may give a similar clinical and histopathological picture. Experts from the International Autoimmune Hepatitis Group (IAHG) have prepared a scoring scale to facilitate the diagnosis of patients with AHI, and a simplified version of this scale (Table 1.), which is more commonly used in everyday medical practice [13].

Table 1.**Simplified criteria for the diagnosis of autoimmune hepatitis (AIH) according to IAHG**

|  |  |
| --- | --- |
| Criterion | Score |
| Autoantibodies |
| ANA or SMA in titer ≥1:40 | 1a |
| ANA or SMA in titer ≥1:80, or anti-LKM1 in titer ≥1:40, or antiSLA/LP present | 2a |
| IgG concentration |
| >ULN (16 g/l) | 1 |
| >1,1 × ULN (18 g/l) | 2 |
| Histopathological picture |
| Typical of AIH | 2 |
| Viral hepatitis excluded | 2 |
| Interpretation: 6 pts - AIH likely; 7-8 pts - AIH certain. |
| And max 2 points for all autoantibodies (does not add up) |
| ULN - upper limit of normal; antibodies: ANA - antinuclear, anti-LKM1 - against liver and kidney microsomal antigen, antiSLA/LP - against liver soluble antigen and liver-pancreas antigen, SMA - against smooth muscle |

Biochemical criteria include an increase in aminotransferases, elevated IgG levels and elevated serum γ-globulin levels. IgG concentrations usually increase selectively and normal immunoglobulin concentrations of IgM, IgA are observed. IgG can also be used as a marker of disease activity [5]. Type 1 AIH (AIH-1) is the predominant type of AIH in both adults and children. Characteristic of this type of AIH is the demonstration of positive antinuclear antibodies (ANA) and/or anti-smooth muscle antibodies (anti-SMA). Type II AIH (AIH-II) is much rarer and is more commonly found in the pediatric population. Antibodies against liver/kidney microsomes type 1 (anti-LKM-1) and/or liver cytosol type 1 (anti-LC-1) are characteristic of this type of AIH [14].

Histopathological examination of a liver slice is a key part of the diagnosis of patients suspected of having AIH. In histopathology, we can see lymphoplasmocytic infiltrates involving the portal zone and peripheral lobular zones of the liver. There may be rosette structures, necrosis of hepatocytes and spider fibrosis [3,5]. A liver biopsy should be performed in every patient to confirm the diagnosis of AIH and to facilitate further therapeutic decisions. Histopathological examination is important because it provides an opportunity to determine the extent of the disease and this will allow us to make a preliminary prognosis for the patient suffering from autoimmune hepatitis [6].

**Progression to cirrhosis**

Progression from autoimmune hepatitis (AIH) to the development of full-blown cirrhosis is a multi-stage process, which is why it is so important to diagnose patients accurately in order to introduce treatment as early as possible and protect against its development and complications.

Describing the progression of changes, we can start with the development of inflammation, which leads to damage to hepatocytes. There is activation of hepatic stellate cells (HSCs), which differentiate into collagen-producing myofibroblasts. In chronic liver disease, and AIH is such, there is a continuous production of extracellular matrix (ECM) by activated myofibroblasts. As fibrosis progresses, scarring of the liver tissue occurs. The liver organ gradually ceases to perform its function [15,16]. The development of cirrhosis is an irreversible process, causing serious clinical consequences such as esophageal varices, ascites, hepatic encephalopathy, hypoalbuminemia, hepatorenal syndrome, hepatopulmonary syndrome and many others [17].

An important fact is that the rate of progression from AIH to cirrhosis can vary depending on many factors, including individual patient characteristics, the presence of comorbidities and the effectiveness of AIH treatment.

Adequate and effective immunosuppressive treatment of AIH, controlling the inflammatory process and delaying progression to cirrhosis play a key role. Regular monitoring and appropriate clinical interventions are essential in the management of patients with this complex condition [18].

**Treatment of AIH**

Adequate and effective treatment of AIH is the basis for avoiding the development of cirrhosis. Treatment consists of reducing the inflammation taking place in the liver, controlling the excessive immune response and maintaining liver function [19]. The main tool is immunosuppressive drugs, but the patient must be properly educated for the treatment to be effective. Maintaining a healthy lifestyle and avoiding substances that are toxic to the liver is an issue that cannot be forgotten when treating a patient with AIH.

We can divide the drug treatment of AIH into two phases:

* induction phase
* maintenance phase.

In the induction phase, glucocorticosteroids and azathioprine are the primary treatment. These drugs can be administered simultaneously ( prednisone + azathioprine) or prednisone can be given as monotherapy [5].

Before initiating azathioprine treatment, thiopurine methyltransferase (TPMT) activity determination can be considered. TPMT is an enzyme that is responsible for the metabolism of thiopurines, one of which is azathioprine. The results of TPMT activity tests are taken into account in azathioprine dosing. Individuals with lower TPMT activity will metabolize the drug more slowly, which may result in side effects and require a change in the administered dose of the drug. Too high a concentration of azathioprine metabolites can cause neutropenia, leukopenia or myelosuppression, so it is important to determine the appropriate TPMT concentration before starting treatment. In patients with normal TPMT, standard doses of azathioprine should be adequate [20].

The corticosteroid drug of choice in AHI is prednisone. Standard doses of prednisone are 60 mg in monotherapy or 30 mg in combination with azathioprine. Prednisone allows rapid reduction of symptoms, transaminases levels and IgG levels. The use of budesonide can be an alternative to prednisone. However, it is important to remember that budesonide works through the same receptor as prednisone, so it is not an option for non-responders to first-line treatment [21]. Budesonide can also be an effective treatment in adolescents and young children [22].

Once remission is achieved, maintenance treatment should be instituted with low doses of prednisone or azathioprine, or a combination of the two [23]. The treatment of AIH is a long-lasting process in which doctor-patient cooperation is required. If standard treatments are ineffective and complications occur, advanced therapies such as liver transplantation may be necessary. However, any choice of treatment must be tailored to the needs of the individual patient [24].

**Summary**

Although autoimmune hepatitis is not a common cause of cirrhosis development, we should not forget to diagnose patients, for AIH. We should evaluate every case of chronic liver disease for AIH, the etiology of which is unknown to us. In clinical diagnosis, the use of the simplified scoring scale prepared by IAHG experts is a great help. In the treatment of AIH, drug therapy remains the first choice: azathioprine or prednisone. Liver transplantation remains the treatment of choice in the most severe cases. Active patient participation in treatment offers a better chance of cure and avoidance of the consequences of the developing disease.

**Disclosures**

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