Chapter 1

An update of Auto Immune Hepatitis:
epidemiology, clinical aspects and treatment

Submitted

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Chapter 1

Abstract

Auto immune hepatitis (AIH) is an immune mediated progressive inflammatory liver disease that predominantly affects middle-aged females but may affect people of all ages. The clinical spectrum of AIH is wide, ranging from absent or mild symptoms to fulminant hepatic failure. The aetiology of AIH is still unknown, but is believed to occur as the consequence of an aberrant immune response towards an unknown trigger in a genetically susceptible host. In the absence of a golden standard, diagnosis is based on the combination of clinical, biochemical and histopathological criteria. Immunosuppressive treatment has been the cornerstone of treatment since the earliest description of the disease in 1950 by Waldenström. Such treatment is often successful at inducing remission and generally leads to normal life expectancy. Nevertheless, there remain significant areas of unmet aetiological and clinical needs including fundamental insight in disease pathogenesis, optimal therapy, duration of treatment and treatment alternatives in those patients unresponsive to standard treatment regimens. Here, we provide an update of the latest trends in epidemiology, clinical course, diagnostics, complications and treatment of AIH.
Introduction

In 1950, Jan Waldenström was the first to describe a chronic form of hepatitis in young women. Subsequently, the disease was found to be associated with other autoimmune syndromes and was later termed “lupoid hepatitis” because of the presence of lupus erythematosus cells and antinuclear antibodies. These observations led to the idea that a loss of immunological tolerance was at the basis of this disease. The term Auto Immune Hepatitis (AIH) was introduced by Mackay and colleagues in 1965 when the concept of autoimmunity was acknowledged at an international meeting.

AIH is now recognized as a relatively rare chronic inflammatory liver disease predominantly affecting females in which a loss of tolerance against hepatic tissue is presumed. Based on the type of serum autoantibodies, two types of AIH can be recognized: type 1 AIH, characterized by antinuclear antibodies (ANA) and/or anti-smooth muscle antibodies (SMA), and type 2 AIH, predominantly found in children and defined by antibodies directed against liver kidney microsomes type 1 (anti-LKM-1) or for anti-liver cytosol type 1 antibodies (anti-LC-1).

Epidemiology

There are few studies that have explored the epidemiology of AIH. The majority of these studies are hampered by the fact that no predefined criteria for disease diagnosis were applied. In some older studies there has been admixture of patients with chronic hepatitis C and finally some of the studies may have been subject to tertiary referral bias. Nevertheless, incidence data are more or less comparable in Western Europe, ranging from 0.8 to 3 per 100,000 with a prevalence ranging from 11 to 24 per 100,000. AIH appears to be less frequent in Asia, with incidence figures ranging between 0.08 and 0.15 in Japan.

Substantially higher prevalence data of 42.9 cases per 100,000 were found in a well defined native Alaskan population although it should be noted that this study involved only a very limited number of patients in a small catchment area. Based on the available studies it is estimated that AIH is the cause of 11-20% of all cases of chronic hepatitis in Western countries. The prevalence of AIH is still gradually increasing. Whether or not this reflects a true rise in incidence, as seen in other immune-mediated diseases like Crohn’s disease, increased awareness of the disease or different diagnostic criteria is unknown. Women are affected more frequently than men with a sex ratio of around 4:1. In women a bimodal age pattern is usually seen, one in the late teens and one around the menopause but it should be stressed that disease can develop in all age groups and both genders.

In women a bimodal age pattern is usually seen, one in the late teens and one around the menopause but it should be stressed that disease can develop in all age groups and both genders.
Table 1: studies of incidence and prevalence of Autoimmune Hepatitis

<table>
<thead>
<tr>
<th>Study and reference no.</th>
<th>year</th>
<th>Cases</th>
<th>Incidence/100.000</th>
<th>Prevalence/100.000</th>
</tr>
</thead>
<tbody>
<tr>
<td>Toda, Japan(^{10})</td>
<td>1997</td>
<td>496</td>
<td>0.8</td>
<td>-</td>
</tr>
<tr>
<td>Whalley, UK(^{120})</td>
<td>2007</td>
<td>200</td>
<td>3.0</td>
<td>-</td>
</tr>
<tr>
<td>Werner, Sweden(^{5})</td>
<td>2008</td>
<td>473</td>
<td>0.85</td>
<td>10.7</td>
</tr>
<tr>
<td>Gronbaek, Denmark(^{7})</td>
<td>2014</td>
<td>1721</td>
<td>1.68</td>
<td>23.9</td>
</tr>
<tr>
<td>Gerven, Netherlands(^{8})</td>
<td>2014</td>
<td>1313</td>
<td>1.1</td>
<td>18.3</td>
</tr>
<tr>
<td>Ngu, New Zealand(^{19})</td>
<td>2010</td>
<td>138</td>
<td>2.0</td>
<td>24.5</td>
</tr>
<tr>
<td>Delgado, Israel(^{21})</td>
<td>2013</td>
<td>100</td>
<td>0.67</td>
<td>11</td>
</tr>
<tr>
<td>Primo, Spain(^{122})</td>
<td>2004</td>
<td>13</td>
<td>1.37</td>
<td>11.61</td>
</tr>
<tr>
<td>Hulburt, Alaska(^{13})</td>
<td>2002</td>
<td>77</td>
<td>-</td>
<td>42.9</td>
</tr>
</tbody>
</table>

Pathogenesis

The etiology of AIH remains unknown and fundamental questions regarding disease pathogenesis remain to be resolved. It is generally believed that disease occurs as the consequence of an exaggerated immune response towards hepatic tissue in a genetically susceptible host\(^{14}\). Such an immune response can occur when effector lymphocyte responses are abundant and inappropriate leading to tissue damage, or, alternatively, when there is a numerical and/or functional defect in regulatory T cells controlling such responses. Whilst abundant pro-inflammatory responses have been identified in most, if not all immune-mediated diseases, it has been very difficult to gain evidence for a primary defect in regulatory T cells in the majority of these diseases. That impaired immunoregulation could partially account for the pathogenesis of AIH is suggested by studies showing that a numerical Treg impairment affects both children and adults with AIH\(^{15-17}\). In addition, it was shown that Tregs from AIH patients at diagnosis are impaired in their ability to control the proliferation of CD4 and CD8 effector cells. More recent studies failed to find either numerical or functional Treg impairments in AIH patients and thus the question as to whether AIH is the result of defective immunoregulation warrants further investigation.

A third, not mutually exclusive mechanism may relate to molecular mimicry, in which immune responses to exogenous pathogens cross-react with structurally similar self-components. Such a response may spark an inflammatory reaction and the resulting hepatocellular injury may give rise to the release of other previously hidden antigens that may further fuel the inflammatory reaction. Exogenous pathogens implicated in this process include, amongst others, the hepatitis C virus, which shares high amino-acid sequence homology with the auto-antigenic target of anti-LKM-1 autoantibodies in AIH-2, cytochrome P4502D6 (CYP2D6)\(^{18, 19}\). Indeed, up to 10% of HCV patients are seropositive for anti-LKM-1. Other proposed triggers include other hepatotrophic viruses, as well as drug induced liver injury caused by antibiotics (including nitrofurantoin and minocycline), statins and anti-TNF agents\(^{20-25}\).
Genetic factors

Genetic factors have long been implicated in disease pathogenesis yet systematic studies addressing the genetic epidemiology of AIH including familial occurrence, disease concordance in twins or ethnic differences in disease prevalence are lacking. Nevertheless, there are several observations that support a genetic basis for AIH. These include the association with other autoimmune diseases with a known genetic basis in up to a quarter of patients. Additionally, associations with alleles of the Major Histocompatibility Complex (MHC) that encode the Human Leucocyte Antigens (HLA) were already described in the late seventies and confirmed and refined thereafter in numerous studies in different ethnic groups. Such associations are found with most autoimmune diseases, most likely because they contribute to the specificity of immune responses. The strongest MHC association is found with the HLA-DRB1 locus, with the haplotypes DRB1*0301 (HLA-DR3) and DRB1*0401 (HLA-DR4) conferring strongest associations with the disease in Caucasians. Intriguingly there is evidence for substantial genetic heterogeneity in AIH with different MHC associations in different ethnic populations. Thus, in Japanese patients HLA-DRB1*0405 is the most important susceptibility allele whereas primary associations with DRB1*0404 were found in Mexican patients. The HLA alleles not only determine overall disease susceptibility but appear also to act as modifiers of the clinical phenotype. For instance, HLA-DR4 was found to be associated with female gender, less severe disease, more common autoimmune disease, and older age of onset.

Despite the fact that the MHC loci confer a 6 to 7 fold increased disease risk, these variants alone cannot explain the genetic predisposition for AIH. Genes outside the MHC have only been studied in candidate gene approaches involving limited numbers, making them prone to overestimation of significance. Most extensively studied is a polymorphism at position +49 in the cytotoxic T lymphocyte antigen-4 (CTLA-4) gene. A recent study in the Netherlands involving a substantial number of patients however observed no significant differences in allele and genotype frequencies of the +49 A/G polymorphism between AIH patients and controls. More recently, genome-wide association studies (GWASs) have emerged as a powerful and unbiased approach for the identification of new genetic susceptibility loci in autoimmune diseases. Very recently this methodology was applied in a large multicentre cohort of type 1 AIH patients. This study confirmed the involvement of the MHC region and identified SH2B3 as the first genetic risk factor outside the MHC region. In addition, several other loci were identified supporting the thesis that AIH has a complex genetic basis.
Clinical features

The clinical spectrum of AIH is wide, ranging from absent or mild symptoms to fulminant hepatic failure\(^4\). AIH should be suspected in all patients with symptoms of liver disease, so that appropriate treatment can be instituted without delay. Up to 40 percent of patients present with acute hepatitis, characterized by right upper-quadrant abdominal pain, fatigue, jaundice and arthralgia\(^5\). However, a fulminant presentation or a long subclinical course with only minimal elevations of liver enzymes and non-specific symptoms, such as arthralgia or fatigue, may be seen\(^12, 46-49\) (Table 2).

Clinical manifestations of AIH may vary among ethnic groups. Thus, non-Caucasian patients (the majority being from African-American descent) had more aggressive disease presentation, lower response to immunosuppressive therapy, and worse outcomes when compared to Caucasian patients\(^4\). Higher rates of cirrhosis were present in Hispanic versus Caucasian patients, and were a trend towards worse survival among Asians\(^50\).

Associated concomitant autoimmune diseases in AIH are common in up to 40% of patients. They included, among others, thyroid disease, diabetes, inflammatory bowel disease and rheumatoid arthritis.

**Table 2: presentation and symptoms in AIH**

<table>
<thead>
<tr>
<th>• Acute hepatitis</th>
<th>• Chronic hepatitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>• hepatomegaly</td>
<td>• splenomegaly</td>
</tr>
<tr>
<td>• spider naevi</td>
<td>• palmar erythema</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>• Non specific symptoms:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• tiredness</td>
</tr>
<tr>
<td>• fever</td>
</tr>
<tr>
<td>• loss of appetite</td>
</tr>
<tr>
<td>• upper abdominal pain</td>
</tr>
<tr>
<td>• arthralgia</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>• Extrahepatic autoimmune disease (most common mentioned):</th>
</tr>
</thead>
<tbody>
<tr>
<td>• thyroiditis 10-23%</td>
</tr>
<tr>
<td>• primary biliary cirrhosis 10-20%</td>
</tr>
<tr>
<td>• diabetes 7-9%</td>
</tr>
<tr>
<td>• primary sclerosing cholangitis 2-8%</td>
</tr>
<tr>
<td>• rheumatoid arthritis 2-5%</td>
</tr>
<tr>
<td>• celiac disease 1-2%</td>
</tr>
</tbody>
</table>

A recent study demonstrates that celiac disease is more common in AIH patients compared to the general population\(^51\). In addition, AIH has features that resemble primary sclerosing cholangitis (PSC) and primary biliary cirrhosis (PBC) and overlap with these disorders are reported in 10-20% and 2-8% of cases, respectively\(^9, 14, 52-55\) (Table 2). So far, there have not
been uniform definitions or diagnostic criteria for the overlap of AIH with PBC or PSC. There is still controversy as to whether these overlap syndromes represent distinct entities or variants of the main autoimmune liver diseases. The presence of features of different diseases can occur simultaneously as well as sequentially in each form of overlap syndromes. AIH and PBC are the most prevalent autoimmune liver diseases. Liver function tests typically show a hepatitic pattern in AIH, and a predominantly cholestatic pattern in PBC; moreover, while an elevation in IgG level is typical of AIH, an increase in IgM is present in the majority of PBC patients. There are no validated scoring systems for the diagnosis of PBC-AIH overlap but most studies have adopted the criteria proposed by Chazouillères et al., in which the diagnosis of the overlap requires the presence of at least two out of three features for each component of the overlap. The PBC criteria comprise: 1) ALP at least twice or GGT at least five times the upper limit of normal (ULN); 2) positivity for AMA, and 3) histological evidence of florid bile duct lesions. The AIH criteria include: 1) ALT at least 5 times ULN, 2) IgG at least 2 times ULN or positivity for SMA, and 3) liver biopsy with moderate or severe periportal or perisepal inflammation.

AIH-PSC overlap syndrome has been described in various reports over the last few decades. AIH-PSC overlap is characterised by ANA and/or SMA seropositivity, hypergammaglobulinaemia and interface hepatitis – all features typical of "classical" AIH – in conjunction with cholestatic biochemical alterations, frequent concurrence of IBD, and histological evolution to fibrous obliteratorive cholangitis, ductopenia, portal tract oedema and/or bile stasis.

**Diagnosis**

The diagnosis is based on the combination of clinical and laboratory findings and histological abnormalities after exclusion of viral causes.

**Laboratory abnormalities**

AIH is suggested by a patient with elevated Alanine-aminotransferase (ALT) and Aspartate transaminase (AST) activity, raised Immunoglobulin G (IgG), high titres of circulating antibodies, negative serum tests and exclusion of toxic hepatitis. However not all these laboratory findings need to be present in an individual patient. Elevation of serum IgG is a common finding in AIH, but normal IgG levels may be found in up to 30% of patients. Auto antibodies are the hallmark of AIH and can constitute an important part of the diagnostic work up. The classic antibodies associated with AIH are Antinuclear antibodies (ANA), antismooth-muscle antibodies (ASMA) and Anti Liver kidney microsomal (LKM-1). About 70-80% of AIH patients have significant titres (≥1:40) of ANA or ASMA and overall 3-4% have anti LKM-1, while up to 20% have none of these antibodies. ANA are the most commonly
found auto antibodies in AIH, yet are rather non-specific since they can be found in a large variety of diseases as well as in healthy individuals. ANA may be the only antibody present or may occur in conjunction with ASMA. ASMA are the second major class of antibodies which have proved useful in the diagnosis of AIH. Although less prevalent than ANA they are more specific. Autoantibody detection not only assists in the diagnosis but also allows the differentiation of AIH into type 1 (ANA and/or SMA positive) and type 2 (anti-LKM-1 and/or anti-liver cytosolic-1 (LC-1) positive). Type 2 AIH accounts for less than 10% of all cases in Northern Europe and North America.

10-30% of patients with AIH will have detectable antibodies to soluble liver antigen (SLA) or liver pancreas antigen (LP). These antibodies are specific for AIH, so may also be useful in the diagnosis. Antibodies to actin and atypical peripheral anti-neutrophilic cytoplasm (p-ANCA) are also frequently seen in type 1 AIH, however their applicability is limited by their lack in specificity.

Liver histology
Liver biopsy is mandatory not only to establish the diagnosis, evaluate disease severity and exclude other causes of hepatitis. There are no individual histological criteria that prove the diagnosis of AIH. Inflammation of hepatocytes at the junction of the portal tract and hepatic parenchyma, known as interface hepatitis (or peacemeal necrose) is the histological hallmark of AIH. It is found in 84-98% of patients, but can also be seen in patients with drug-induced and viral hepatitis.

Lymphocytes, plasma cells and histiocytes surround individual dying hepatocytes at the portal-parenchymal interface and in the lobule. Though plasma cells are usually abundant at the interface and throughout the lobule, their presence in low number does not exclude the diagnosis of AIH and may be absent in up to one third of the patients.

In a recent study, emperipolesis and rosette formation were found superior histological predictors of AIH when compared to the classical hallmark features of interface hepatitis and plasma cells.

Diagnosis scoring system
In the absence of a golden standard for the diagnosis AIH, diagnostic scoring systems have been developed that support the diagnosis in the majority of patients. The IAIHG scoring system, originally published in 1993 and revised in 1999, was developed as a search tool to ensure comparability of study populations. Despite a high degree of sensitivity (100%) and specificity (90%), these criteria have been proven impractical in the day to day clinical practice.

In 2008 the IAIHG produced a simplified system for the diagnosis of AIH which is less complex and enhances applicability in clinical practice. This system is based on four variables:
presence and level of antibodies, IgG concentration, typical histological features and absence of viral markers (Table 3). Recently three retrospective studies report that the simplified scoring system performs with high specificity (97-99%) and lower sensitivity (81-88%) when compared to the original diagnostic criteria yet requires further prospective validation\textsuperscript{72, 76, 77}.

\textbf{Table 3: simplified Diagnostic criteria for AIH} \textsuperscript{75}

<table>
<thead>
<tr>
<th>Variable</th>
<th>Cutoff</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANA or ASMA</td>
<td>≥1:40</td>
<td>1</td>
</tr>
<tr>
<td>ANA or ASMA or LKM-1 or SLA</td>
<td>≥1:40</td>
<td>2</td>
</tr>
<tr>
<td>IgG</td>
<td>&gt;Upper normal limit</td>
<td>1</td>
</tr>
<tr>
<td>Liver histology (evidence of hepatitis is a necessary condition)</td>
<td>Compatible with AIH</td>
<td>1</td>
</tr>
<tr>
<td>Liver histology (evidence of hepatitis is a necessary condition)</td>
<td>Typical AIH</td>
<td>2</td>
</tr>
<tr>
<td>Absence of viral hepatitis</td>
<td>yes</td>
<td>2</td>
</tr>
</tbody>
</table>

≥6: probable AIH
≥7: definite AIH

Abbreviation: ANA, Antinuclear antibodies; ASMA, anti-smooth-muscle antibodies; LKM-1, Anti Liver kidney microsomal IgG, Immunoglobulin G.

\textbf{Treatment}

\textit{Indication of treatment}

The short and long term efficacy of immune suppression in patients with AIH has been demonstrated unequivocally. When left untreated, as many as 40 percent of untreated patients will die within six months of diagnosis\textsuperscript{78}. When treated adequately, the 20-year life expectancy for all treated patients exceeds 80%, and survival is similar to that of age and sex matched normal subjects from the same geographical region\textsuperscript{79}.

Updated treatment guidelines have recently been issued by the American Association for the Study of Liver Diseases (AASLD) in 2010\textsuperscript{4} and the British Society of Gastroenterology in 2011 (BSG)\textsuperscript{80}. Patients with AST levels 10-fold the upper normal limit, or fivefold the upper normal limit in conjunction with IgG levels at least twice the upper normal limit, or histological features of bridging necrosis or multiainar necrosis, should be offered immunosuppressive treatment because of clear survival benefit (Table 4). Patients not satisfying these criteria must be individualized and treatment should be based on clinical judgement\textsuperscript{4}.
Table 4: indication for treatment of AIH (adapted from Manns et al 4)

<table>
<thead>
<tr>
<th>Absolute</th>
<th>Relative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum AST≥10 fold ULN</td>
<td>Symptoms (fatigue, arthralgia, jaundice)</td>
</tr>
<tr>
<td>Serum AST≥5 fold ULN and IgG level≥twice normal</td>
<td>Serum AST and/or IgG less than absolute criteria</td>
</tr>
<tr>
<td>Bridging necrosis or multiacinar necrosis on histological examination</td>
<td>Interface hepatitis</td>
</tr>
</tbody>
</table>

Abbreviation: AST, Aspartate transaminase; ULN, upper limit normal; IgG, Immunoglobulin G.

Standard treatment

Current treatment strategies for AIH consist of an induction course with prednisone and frequently include subsequent addition of azathioprine (AZA) as steroid-sparing maintenance therapy. Prednisone is initiated at a dose of 1 mg/kg with a maximum of 60mg per day in monotherapy or a maximum of 30mg/day in combination treatment. After AST and ALT normalize, prednisone alone can be reduced by 10mg per week until a dose of 20mg. Patients treated with combination therapy can reduced prednisone by 5mg per week until 15mg. A slower reduction is advised after this point. AZA can the be used at a dose 1-2 mg/kg/day for maintenance treatment either alone or in combination with low dose prednisone. A recent review based on available randomised controlled trials has shown that prednisone monotherapy and prednisone in combination with AZA are both viable induction therapies for AIH, while maintenance therapy prednisone and AZA and Monotherapy AZA are superior to prednisone monotherapy. The treatment of AIH with corticosteroids and AZA is accompanied by the risk of many side effects on both drugs. The side effects of long term treatment with corticosteroids are well established; acne, moon shape face, striae, weight gain and loss of bone density. Adverse events of thiopurines are frequent and generally occur shortly after the start of therapy. They include allergic reactions, nausea, flu-like illness, malaise, fever, rash, abdominal pain, pancreatitis, hepatotoxicity, and myelosuppression. The principal side effects of AZA are cytopenia and liver test abnormalities.

Remission and relapse

Remission of previously symptomatic patients is defined as a complete normalisation of all inflammatory parameters, including AST, ALT, bilirubine, IgG, recovery from symptoms and inactive liver histology. In 80-90% of patients with moderate/severe AIH, serum ALT falls after starting treatment. Usually a fall is seen within two weeks. As transaminase fall, clinical symptoms revolve and liver functions shows marked improvement within 3-6 months after starting prednisone treatment either with or without AZA. There is no prescribed minimum or maximum duration of treatment. Because histological improvement lags behind clinical and biochemical improvement by 3-8 months, treatment should be continued for at least this period. The AASLD guidelines recommend drug
withdrawal after at least 2 years treatment, when serum liver and immunoglobulin levels have been repeatedly normal. Liver biopsy prior to termination of treatment is preferred. Relapse is characterized by an increase in ALT levels (three times upper normal limit) and/or increase of serum IgG level to more than 2 g/L following tapering of steroid doses or after complete withdrawal of immunosuppression. Although some patients may remain in remission after treatment withdrawal, most require long-term maintenance treatment. Literature from the 1970s indicated a high risk of relapse after drug withdrawal, but this was later disputed and it was recommended that drugs withdrawal should be attempted. A more recent retrospective analysis observed that relapse after drug withdrawal occurred in almost all patients with AIH when immunosuppressive medication was discontinued. Relapse occurred despite prior attainment of complete remission, including a histological inactive follow up biopsy prior to tapering in a subgroup of patients. In patients who have relapsed once, a subsequent attempt to withdrawal therapy was invariably associated with the re-occurrence of a relapse. Since repeated relapses were associated with a poorer long term prognosis patients should receive life long treatment. A lifelong follow up should occur in patients who successfully stopped immunosuppression, while a relapse can occur 10 years later.

Alternative treatment
In up to 10% of AIH patients, the therapeutic strategy of prednisone and AZA proves ineffective, due to lack of clinical response or intolerable side effects. In patients who fail on standard therapy, alternative immunosuppressive treatments have been tried with encouraging results. Cyclosporine, tacrolimus, methotrexate, cyclophosphamide and mycophenolate mofetil have been tried, with varying degrees of success, as a replacement for AZA. In a small recent study patients suffering from ineffectiveness or intolerance to AZA or mercaptopurine, due to unfavourable thiopurine metabolism, allopurinol was added to the treatment. The combination of low dose thiopurines and allopurinol proved an effective and well-tolerated alternative in the treatment of AIH. Larger and controlled studies are needed to confirm these outcomes.

As an alternative for prednisone, budesonide is receiving considerable attention. In two recent studies oral budesonide, in combination with azathioprine, induces and maintains remission in patients with noncirrhotic AIH, with a low rate of steroid-specific side effects. Given the short trial duration and the fact that no follow up date were presented, routine use is not currently recommended.
Complications and prognosis

Complications in AIH are similar to those seen in other progressive liver diseases and in rare cases AIH presents by the occurrence of hepatic encephalopathy. Liver fibrosis is of the present and a subgroup of patients have already cirrhosis at presentation, indicating that the disease has gone unrecognized for a considerable period of time prior to diagnosis. Without treatment, as many as 40% of patients will die within 6 months of diagnosis. In some patients without proper treatment, AIH progresses to cirrhosis and eventually Hepatocellular carcinoma (HCC). HCC however occurs less frequently in AIH compared to patients with chronic viral hepatitis. The presence of cirrhosis at presentation or during treatment and the frequent need for long-term immunosuppressive treatment have been regarded as risk factors for malignant transformation. In addition risk factors for HCC furthermore include male gender, advanced stage disease, portal hypertension as ascites and esophageal varices. HCC occurs in 1-9% of AIH patients. Imaging with ultrasonography or computed tomography should be performed every 6-12 months. For patients who progress to liver failure, liver transplantation may be considered. When AIH is indicated for transplantation, transplanted patients, practically compared to other chronic liver diseases, have an excellent 5 year survival of between 78-91%. The recurrence rate of AIH after initial successful transplantation are problematic issues and occurs in around 30% of patients.

Conclusion

AIH is a relatively rare disease of unknown aetiology. Many factors contribute to the diagnosis, which is characterized by a female predominance, histological features of periportal hepatitis in the absence of viral markers, hypergammaglobulinaemia, the presence of auto antibodies in serum, plasmacellular infiltrates and an optimal response to steroids in most patients. Due to large heterogeneity of the clinical, laboratory, serological, histological and genetic features of the disease, AIH might be underestimated or unrecognised. The clinical spectrum of AIH is wide, ranging from absent or mild symptoms to fulminant hepatic failure. AIH generally responds to immunosuppressive treatment which should be instituted as soon as the diagnosis is made. For most patients life long treatment is indicated. In patients in whom all treatment attempts fail liver transplantation remains a final option.

AIH remains a major diagnostic and therapeutic challenge. Growing insights into the clinical presentation of AIH highlights the importance of evaluation of the current diagnostic criteria, role of genetic, and environmental factors, as well as the development of new treatment.
Reference List

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