European Reference Network
for rare or low prevalence complex diseases
Network Hepatological Diseases (ERN RARE-LIVER)

Autoimmune Hepatitis (AIH)

Leaflet for adult physicians

Description

Autoimmune Hepatitis (AIH) is a chronic liver disease characterised by increased serum transaminases and immunoglobulin G, circulating autoantibodies and infiltration of immune cells on liver histology. Its pathogenesis is largely unknown, but an autoimmune reaction directed against hepatocytes is assumed. Most patients need life-long immunosuppressive treatment to prevent the development of end-stage liver disease. Following induction of remission with corticosteroids, maintenance therapy with azathioprine can be effective in patients with AIH type 1, but for most patients with AIH type 2 and patients with autoimmune sclerosing cholangitis (ASC) long-term combination therapy of azathioprine and low dose steroids is needed. Patients not responding or intolerant to this standard treatment need treatment with second- or third-line immunosuppressants. The treatment goal is normalization of transaminases and immunoglobulin G within 6-12 months.

Genetics

Genetic variations are relevant to develop and maintain the autoimmune reaction in AIH. Multiple genes may interact to determine both disease risk and phenotype. Allelic variants of the DRB1-genotype in the HLA locus are associated with susceptibility for AIH (HLA-DR3 and -DR4 in Europe and North America). Associations with single nucleotide polymorphisms within non-HLA genes have also been identified, but their relevance is less clear.

Clinical presentation

Patients with AIH may be asymptomatic or present with a wide and heterogenous spectrum of symptoms. Thus, in more than 20% of patients an increased ALT detected by coincidence leads to the diagnosis, whereas up to 50% of patients present with jaundice and malaise and another 25% have cirrhosis at the point of diagnosis. Probably 5-10% of cases present with acute severe AIH leading to acute liver failure and may require liver transplantation.

Risk factors

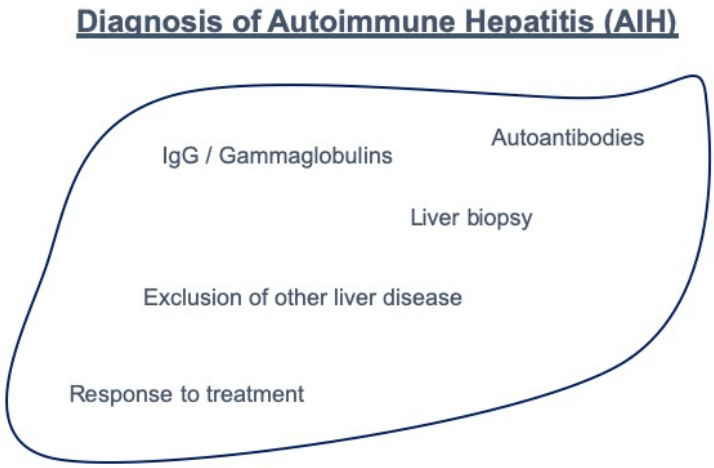
Female gender, other autoimmune diseases in the patient or in relatives and HLA-DRB1 genotypes are risk factors for AIH. Environmental factors have not been consistently linked to AIH, however a variety of hepatotropic viral infections and drugs have been proposed as potential triggers of AIH. Whether endogenous factors such as the hormonal status, pregnancy or intestinal dysbiosis are of importance, is not clear.

Symptoms

The most frequent symptoms are nausea, upper abdominal discomfort, fatigue, jaundice and arthralgias. In cases with a more insidious presentation, fatigue may be the only symptom. In patients having already developed liver cirrhosis, spider naevi, ascites or variceal bleeding may be the first symptoms.

Diagnosis

Elevation of transaminases and immunoglobulin G and the detection of autoantibodies (anti-nuclear antibodies, ANA, anti-smooth muscle antibodies, anti-SMA, anti-soluble liver antigen/liver-pancreas antibodies, anti-SLA/LP and in children and young patients also liver kidney microsomal type 1-antibodies, anti-LKM-1, and anti-liver cytosol type 1-antibodies, anti-LC1) are suggestive of AIH. In children, cut-off for positivity of ANA, anti-SMA and anti- LKM-1 is clinically significant at a lower dilution than in adults. A liver biopsy must be performed for the diagnosis of AIH since certain histologic changes are characteristic, although not specific for AIH. A typical histological feature is the presence of interface hepatitis and portal inflammation with predominantly plasma cells and lymphocytes. Acute viral hepatitis, drug-induced liver injury (DILI), alpha-1-antitrypsin deficiency and Wilson's Disease are important differential diagnoses for the acute presentation of AIH and should be excluded. Every child diagnosed with AIH should undergo magnetic resonance cholangio-pancreatography (MRCP) in the diagnostic work-up to screen for sclerosing cholangitis.



Management

To induce remission of AIH, treatment with prednisolone is needed. In severe cases, treatment should not await biopsy results. In case of robust clinical and biochemical response to steroid treatment, maintenance of remission with azathioprine is added and steroids are tapered. To avoid steroid-related side effects, budesonide can be an alternative to prednisolone for non-cirrhotic patients. There is more experience with budesonide in adult than in paediatric AIH patients. In general, lifelong immunosuppression is needed for most patients. This implies close monitoring of patients to screen for adverse events due to immunosuppressive treatment, such as problems with growth, obesity, osteopenia/osteoporosis, depression, non-melanoma skin cancer, cataract/ glaucoma, bone marrow toxicity, infections and others.

A minority of patients will experience chronic AIH-associated arthralgias or fatigue, but most well-treated patients will be asymptomatic and have excellent prognosis when they are in biochemical and histological remission. Patients with cirrhosis should be monitored for cirrhosis-related complications, however, in some patients reversal of liver fibrosis is observed. Patients with decompensated cirrhosis should be evaluated for liver transplantation.

Patients not responding sufficiently to or not tolerating standard treatment, should be offered second- or third-line therapy in specialized centres. Depending on the preferences of the local centre, the drugs in use are mercaptopurine, mycophenolate mofetil, tacrolimus, infliximab, rituximab, ciclosporin, mTOR inhibitors and others.

Vaccinations should be offered to patients in line with national vaccination programmes. However, the programme may be adjusted, as the response may be enough if vaccinations are administered during maintenance therapy. Immunisation against viral hepatitis A infection and annual influenza vaccination is advised. If vaccination against Hepatitis B is not a part of the national vaccination programme, patients should also be offered this. It may be necessary to check antibody response. In general, vaccination with live attenuated vaccines should be avoided for patients under immunosuppressive treatment.

Complications

Patients who do not respond adequately to treatment are at risk of progression to cirrhosis. In cirrhotic patients, standard screening for hepatocellular carcinoma should be performed. Side effects due to immunosuppressive treatment should be screened for regularly.

Autoimmune hepatitis in the paediatric and adolescent patients

AIH can occur in any age group, even in infancy. The diagnosis may be a challenge:

- The presentation of AIH is often more aggressive than in adults
- Approximately one in five children with AIH have associated autoimmune diseases such as inflammatory bowel disease (IBD), celiac, thyroid or rheumatic disease
- An overlap syndrome between AIH and sclerosing cholangitis (and IBD) occurs more often in children than in adults. Every child diagnosed with AIH should undergo MRCP in the diagnostic work-up
- Diagnostic autoantibody titres are often lower than the required titres for the diagnosis of AIH in adults, and therefore the diagnostic criteria vary between adult and children
- Autoantibodies other than SMA are more frequent in children and adolescents (anti-LC1 and LKM-1), so called AIH type 2
- Liver biopsy often has a more mixed histological picture

The treatment of paediatric and adolescent AIH patients differs:

- The child is growing, this must be taken into consideration when treatment strategies are made
- The side effects may be different compared to adults
- There is a significant chance of relapse especially during adolescence and this is frequently due to non-adherence
- In adolescents, non-adherence can be a big challenge, requiring a multidisciplinary approach by medical doctors, paramedics and psychologists familiar with the care for teenagers and young adults. Transition programmes that include child/teenage education should start as soon as possible, to help them adjust to adult care as well as take responsibility for their own disease and minimise the risk of relapse due to non-adherence.

Special considerations need to be considered for diagnostic investigations in children and teenagers such as:

- Liver biopsy needs general anaesthesia/sedation
- MRCP needs anaesthesia/sedation in young children, usually up to 6-7 years of age.

The completion of the basic vaccination programme and the disease specific immunisation recommendations for children and teenagers under immunosuppressive therapy require specialist input.

Therefore, the care for children and adolescent with AIH needs to be coordinated by a paediatric hepatologist or a paediatric gastroenterologist who has been trained in paediatric hepatology.

CPMS

If you wish to discuss an AIH patient with experts from the ERN, you can upload cases to the CPMS: https://cpms.ern-net.eu/login/.

The CPMS is essential for interaction between healthcare professionals and experts on clinical decision making and is provided by the European Union to all ERNs. CPMS supports online multidisciplinary meetings (tele-boards) to discuss patients with diagnostic or therapeutic dilemmas in need of expert consultation. CPMS offers the opportunity to upload and share clinical data of patients and pictures such as histological slides or MRI images. Importantly, this is fully in line with European data protection law. It is obligatory to inform patients about CPMS and obtain their informed written consent before their data are entered into the system (see CPMS Privacy Statement published by the European Commission on 14 December 2017). The consent form is available in all EU languages in CPMS.