Autoimmune Hepatitis

Autoimmune hepatitis (AIH) is a chronic disease of unknown cause, characterised by continuing hepatocellular inflammation and necrosis, which tends to progress to cirrhosis. Immune serum markers are often present and the disease is often associated with other autoimmune diseases.

- AIH is associated with the complement allele C4AQO and with the HLA haplotypes B8, B14, DR3, DR4, and Dw3.
- The autoantibodies present include antinuclear antibody (ANA), anti-smooth muscle antibody (ASMA), anti-liver-kidney microsomal-1 (anti-LKM-1) antibody, antibodies against soluble liver antigen (anti-SLA), antimitochondrial antibody (AMA) and antiphospholipid antibodies.

AIH is an heterogeneous disorder and it can be divided into two types, depending on which autoantibodies are present:

- **Type 1:** associated with the presence of ASMA or ANA. Accounts for about 75% of patients.\(^1\)
- **Type 2:** associated with the presence of either anti-LKM-1 or anti-liver cytosolic-1 (anti-LC-1) antibodies.\(^2\)

AIH may have cholestatic features that are outside the classical phenotype and resemble findings in other autoimmune liver diseases. These cholestatic phenotypes are called ‘overlap syndromes’.\(^3\)

Juvenile AIH is a progressive inflammatory liver disease, affecting mainly young girls from infancy to late adolescence, and characterised by active liver damage, with high serum activity of aminotransferases, raised immunoglobulin G levels, high titres of serum non-organ-specific and organ-specific autoantibodies, and by interface hepatitis on liver biopsy.\(^4\)

**Epidemiology**

- The prevalence of AIH in Europe is estimated as being in the range of 10-17 cases per 100,000 persons.\(^5\)
- AIH occurs worldwide with a low and probably underestimated prevalence. Although it typically affects young and middle-aged women, it can occur in both sexes and can affect all age groups.\(^6\)

**Presentation**

Presentation can be acute, severe (fulminant), asymptomatic or chronic.\(^7\)

Subclinical disease often precedes the onset of symptoms and many patients have histological evidence of cirrhosis at the onset of symptoms. Common symptoms include:

- Fatigue, myalgia, mild pruritus.
- Nausea (often a prominent symptom).
- Upper abdominal discomfort.
- Anorexia, diarrhoea.
- Arthralgias.
- Skin rashes (including acne), hirsutism.
- Oedema.
- Amenorrhea.
- Chest pain (pleuritis).
- Weight loss and intense pruritus (unusual).
Signs

Common findings on physical examination are as follows:

- Hepatomegaly.
- Jaundice (around 50% of patients).
- Splenomegaly.
- Spider angiomata.
- Ascites.
- Encephalopathy.

Investigations

No pathognomonic features exist for AIH and therefore the diagnosis rests on a combination of compatible biochemical, immunological and histological features together with exclusion of other liver diseases.\[5\]

Diagnosis of autoimmune liver disease requires the exclusion of common viral, drug-induced and metabolic liver disease. The classical features of AIH are elevated aminotransferases, raised IgG-positive auto-antibodies, and interface hepatitis with portal plasma cell infiltrate on biopsy. However, the histology findings are not specific for the diagnosis of AIH.\[8\]

- Autoantibodies (see above).
- Serum protein electrophoresis and quantitative immunoglobulins:
  - An IgG-predominant polyclonal hypergammaglobulinaemia is a common finding in patients with untreated AIH.
  - Increased gammaglobulin and IgG levels are found in around 85% of patients.
  - Immunoglobulin levels typically return to normal during treatment.

- Aminotransferases:
  - Serum aminotransferases: aspartate aminotransferase (AST) and alanine aminotransferase (ALT) are usually elevated at initial presentation.
  - Aminotransferase values correlate poorly with the degree of hepatic necrosis but very high levels may indicate acute hepatitis or a severe flare of pre-existing disease.
  - Continued elevation of the aminotransferases during therapy is a reliable marker for ongoing liver inflammation but active liver inflammation is present in more than 50% of patients with normal LFTs. Biochemical remission may precede true histological remission by 3-6 months.
  - Serum aminotransferases may normalise either on treatment or spontaneously, even with continuing severe hepatic inflammation on biopsy.

- Serum alkaline phosphatase is normal or only mildly raised. A more than two-fold elevation suggests an alternative or additional diagnosis.
- Hypoaalbuminaemia and prolongation of prothrombin time are markers of severe hepatic synthetic dysfunction.
- FBC and blood film: findings include mild leukopenia, normochromic anaemia, Coombs-positive haemolytic anaemia, thrombocytopenia, eosinophilia.
- Imaging studies are not usually helpful in reaching a definitive diagnosis of AIH but may suggest the presence of active inflammation or necrosis. The appearance of an irregular nodular liver may confirm the presence of cirrhosis. Imaging studies may also be used to rule out the presence of hepatocellular carcinoma.

- Liver biopsy:\[9\]
  - Liver biopsy is the most important diagnostic procedure in patients with AIH.
  - Liver biopsy should be performed as early as possible in all patients with acute hepatitis who are thought to have AIH. Confirmation of the diagnosis enables initiation of treatment at an early stage in the disease process.
  - Liver biopsy also provides information on prognosis. Up to a third of patients have cirrhosis at presentation.\[1\]
  - Patients with cirrhosis and those with bridging necrosis at diagnosis have a poorer prognosis than those without.

Associated diseases

Concurrent autoimmune disorders occur in approximately 40% of patients, particularly autoimmune thyroid disorder.\[10\]

- Haematological: hypersplenism, autoimmune haemolytic anaemia, pernicious anaemia, idiopathic thrombocytopenic purpura, eosinophilia.
- Gastrointestinal: inflammatory bowel disease, coeliac disease.
- Proliferative glomerulonephritis.
- Fibrosing alveolitis.
- Pericarditis and myocarditis.
- Endocrine: Graves’ disease, autoimmune thyroiditis, type 1 diabetes mellitus.
- Rheumatological: rheumatoid arthritis and Felty's syndrome, Sjögren's syndrome, systemic sclerosis, mixed connective tissue disease, leukocytoclastic vasculitis, febrile panniculitis.
- Erythema nodosum.
- Lichen planus.
- Uveitis.

Management\[5\]
Patients with moderate or severe inflammation (defined as one or more of serum AST >5 times normal, serum globulins >2 times normal, liver biopsy showing confluent necrosis) should be offered immunosuppressive treatment. Patients with symptoms, established cirrhosis on biopsy and younger patients should also be considered for treatment with immunosuppressive treatment. There is less proven benefit of treating older, asymptomatic patients with mild AIH. These patients should be monitored regularly. The target for remission therapy should be normalisation of serum AST/ALT, gammaglobulin, IgG and, ideally, histological evidence of cessation of active liver inflammation.

Prednisolone in conjunction with azathioprine is the treatment of choice in patients with AIH. Prednisolone alone is sometimes used. Corticosteroid therapy induces clinical, laboratory and histological improvements in 80% of patients with AIH. One study showed that budesonide plus azathioprine achieved normalisation of serum transaminases more quickly and had fewer side-effects compared with prednisolone plus azathioprine. This regime may be considered in non-cirrhotic patients with severe steroid-related side-effects such as psychosis, poorly controlled diabetes or osteoporosis. Other drugs have been used: Azathioprine intolerance is the main indication for mycophenolate use but it can also be used as a first-line therapy. Ciclosporin A and tacrolimus have been tested for non-responders or relapers. Rituximab may be used as salvage therapy. Anti-tumor necrosis factor-alpha agents may be used for incomplete responses or non-responders. Methotrexate is possibly an alternative for induction of remission and maintenance in refractory patients. Cyclophosphamide has been included in the induction regimen with corticosteroids.

Liver transplantation: Liver transplantation is indicated for terminal phases of autoimmune hepatitis. Therapeutic advances have reduced the need for transplantation for AIH. Recurrence of AIH may occur after liver transplantation.

Monitoring
- Patients should be tested for hepatitis A and B immunity and vaccinated if needed.
- Regular blood testing including LFTs, glucose and FBC should be performed.
- All patients should receive calcium and vitamin D supplements.
- Dual-energy X-ray absorptiometry (DEXA) scans should be performed prior to starting steroids and repeated at 1- to 2-yearly intervals.
- Screening for glaucoma and cataracts should be considered after 12 months of prednisolone treatment.

Complications
- Hyperviscosity syndrome secondary to high IgG levels may occur.
- Hepatocellular carcinoma may occur. It is more common in patients with cirrhosis. There is a 10-20% risk of hepatocellular carcinoma in patients with cirrhosis.
- Six-monthly surveillance is recommended to be undertaken in otherwise healthy patients with cirrhosis, using ultrasound and serum alpha-fetoprotein.

Prognosis
- Without treatment, nearly 50% of patients with severe AIH die in approximately five years.
- Outlook for treated patients with AIH is generally very good.
- However, presentation and outcome are variable.
- Some patients receive a maintenance dose of azathioprine or azathioprine and prednisolone which has been shown to reduce the risk of relapse.
- Cirrhosis develops in up to 50% of patients with AIH.

Further reading & references
5. Guidelines for the Management of Autoimmune Hepatitis; British Society of Gastroenterology (May 2011)

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