AUTOIMMUNE HEPATITIS

Chronic hepatitis is often a difficult condition to manage.

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Henry Hairwadzi's main research interest is chronic hepatitis, with his current focus area being the immunogenetics and pathogenesis of autoimmune liver diseases in the non-Caucasoid populations of South Africa, the management of bone disease in chronic hepatitis and liver disease in HIV-viral hepatitis co-infection. His postgraduate work focuses on the clinico-pathological features of autoimmune hepatitis in South Africa.

HISTORY AND CLINICAL DEFINITION

Chronic hepatitis is defined as an inflammatory condition of the liver continuing without improvement for at least 6 months.[1] Terminology such as chronic active and chronic persistent hepatitis came into use in the 1960s when the first attempts at classifying chronic hepatitis began. In the 1990s nomenclature meetings by the International Working Party reclassified chronic hepatitis by aetiology. The accepted terms are summarised in Table I.

Table I. **Current aetiological nomenclature of chronic hepatitis[1]**

Well-established causes	**Differential diagnosis**
Viral hepatitis	Resolving acute hepatitis
• Hepatitis B	• Less than 6 months' duration
• Hepatitis B & D	• Any cause
• Hepatitis C	Wilson disease
Drug-induced hepatitis	Alpha-1-antitrypsin deficiency
Autoimmune hepatitis (AIH)	Haemochromatosis
• Type 1 (classic) autoimmune hepatitis	Alcoholic hepatitis
• Type 2 autoimmune hepatitis	Non-alcoholic steatohepatitis
• Cryptogenic steroid-responsive hepatitis	Primary biliary cirrhosis (PBC)
Cryptogenic hepatitis	Primary sclerosing cholangitis (PSC)
• Unclassified as to viral or autoimmune	Graft-versus-host disease

Autoimmune hepatitis (AIH) is a form of chronic hepatitis that is characterised by the presence of liver-associated autoantibodies, raised gammaglobulins and interface hepatitis with a lympho-plasmacytic infiltrate on liver histology.

Waldenström's initial description of the disease in 1950 was of young women with raised plasma globulins, a plasma cell infiltrate and cirrhosis on histology. Mackay introduced the term lupoid hepatitis in 1956 following his demonstration of the lupus erythematosus cell phenomenon in AIH patients. As a result AIH was for a time thought to be part of the systemic lupus erythematosus (SLE) spectrum of disease.[2]

CLINICAL PRESENTATION

AIH affects all races and age groups with a female preponderance; locally this ratio is 6:1. AIH is well documented from as young as 2 years to as old as 78 years. With improved life expectancy in the developed world, AIH in the elderly is an increasingly recognised condition.[3] Local data from the MRC/UCT Liver Centre show 3 major incidence peaks at ages of 10, 30 and 60 years, seen across both sexes and all ethnic groups.[4] Although the disease clearly occurs in black Africans, AIH is poorly documented in Africa. Our local experience shows that the disease occurs frequently in the non-Caucasoid populations, with 12% of

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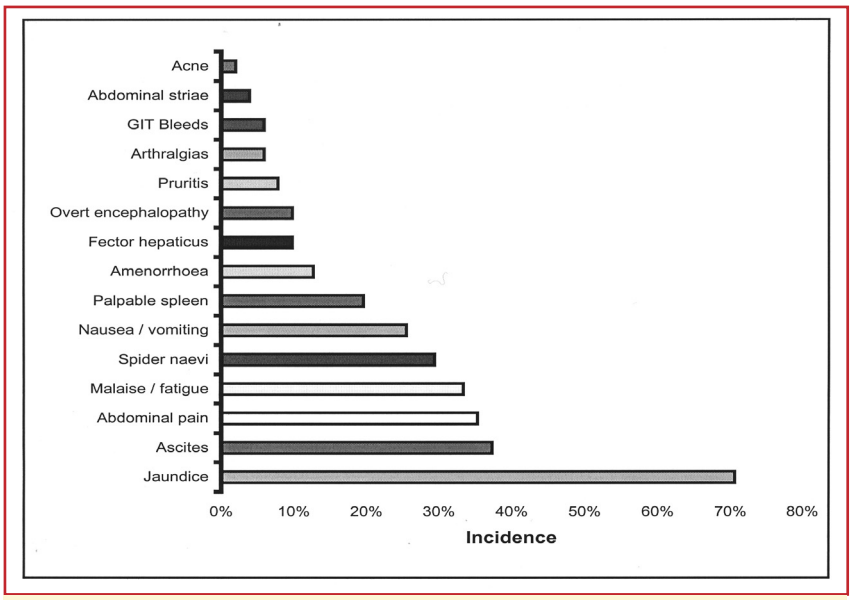

Fig.1. AIH clinical signs and symptoms at first presentation: MRC/UCT Liver Research Centre data.

the clinic cohort of AIH patients being black Africans and 57% non-Caucasoid.[5] Most of these patients have advanced liver disease, with 46% cirrhotic at presentation. It is difficult to separate late presentation due to socio-economic and health care access factors from aggressive disease with more severe injury. Reports from North America in the non-Caucasoid populations are equally scanty. A USA report following up 27 African American patients with AIH suggests that this group might have a more severe disease that requires higher doses of steroids.[6] The signs and symptoms at presentation are varied and range from nonspecific abdominal pains to the more liver-specific problems of jaundice and ascites (Fig. 1).

In children and young adults there is often a preceding history of recurrent episodes of hepatitis and/or jaundice that improved spontaneously. Up to 5% of young patients seen at the MRC/UCT Liver Centre have this type of presentation with repeated negative markers for viral hepatitis during the recurrent episodes of hepatitis. A diagnosis of AIH is often not considered until clinical decompensation occurs, usually with fatal consequences.

AIH may present for the first time in pregnancy and should be part of the diagnostic work-up of liver disease in pregnancy. Previously, concerns about the teratogenic potential of azathioprine often resulted in a recommendation of termination of pregnancy. Recent prospective studies have shown that pregnancy can occur without major complications in the majority of patients, and termination is rarely justified.[7] Termination is considered in advanced liver disease with cirrhosis where there is a high risk for haemodynamic compromise in the third trimester.

PATHOGENESIS

Although the precise cause of AIH remains unknown, the last 50 years have seen major advances in the understanding of the immune and pathological processes involved. An inherent genetic predisposition is central to the development of autoimmunity. AIH is associated with particular human leukocyte antigen (HLA) profiles in the different population groups in which it has been studied. HLA DR3 and 4 are the susceptibility alleles seen in North America and Europe. Locally DR3, 4 and 13 appear to be equally distributed among the non-Caucasoid population.[5]

The genetic susceptibility, when combined with various environmental and immune regulation abnormalities, leads to disease. The environmental factors appear to act primarily through molecular mimicry through the formation of neoantigens that result in the cross-recognition of self epitopes and microbial/neoantigen epitopes. A number of viruses and drugs have been reported as causes of a chronic hepatitis that is indistinguishable from the classic *de novo* AIH. Immune regulation abnormalities involving T-cell co-stimulation and immune cytokine pathways are well described. Gene polymorphisms of the cytotoxic T lymphocyte antigen 4 (CTLA-4) that impair the T-cell co-stimulation signal are well described in Caucasoid populations with AIH and primary biliary cirrhosis (PBC).[8] Similar associations have been documented in autoimmune diseases such as Grave's disease, insulin-dependent diabetes mellitus and SLE. In South Africa our preliminary data show no significant association with AIH, suggesting that perhaps this association may be of importance only in certain Caucasoid populations.[9]

DIAGNOSIS

The diagnosis remains one of exclusion, as there is no single specific and sensitive diagnostic marker for AIH. There has to be careful use of the biochemistry, viral serology, liver-associated autoantibodies, clinical and drug history and liver histopathology when making the diagnosis. The International AIH group has put together diagnostic

Table II. **PBC and PSC overlap syndromes with AIH**

PBC-AIH overlap	PSC-AIH overlap
• High ALT, ALP, GGT	• High ALT, ALP, GGT
• High IgG	• High IgG
• Positive AMA, ANA and/or SMA	• Negative AMA; positive ANA and/or SMA
• DR3 positive	• Children +++, adults
• Adults +++	• Abnormal ERCP
• Normal ERCP	• Moderate interface hepatitis
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criteria that give numerical scores to a number of biochemical, epidemiological, serological and clinical factors to determine the probability of a diagnosis of AIH.[10] The system is particularly important for clinical research reporting.

Classification of AIH

Based on the autoantibody status, AIH is classified into type 1 and 2. The discovery of the soluble liver antigen (SLA) led to the description of a type 3 but this has now been shown to be part of type 1 AIH with a more severe clinical course. The presence of smooth-muscle antibody (SMA) and/or antinuclear antibody (ANA) characterises type 1 AIH. This occurs across all age groups and is the most prevalent, accounting for 95 - 98% of AIH cases. Type 2 AIH is characterised by the presence of anti-liver, kidney microsomal type 1 antibody (anti-LKM-1). This is commoner in children and in general tends to have a more aggressive course. At the MRC/UCT Liver Centre only 2% of the AIH patients are anti-LKM-1-positive and in the type 1 group; 45.1 % are ANA-positive, 27.5% SMA-positive and 25.5% are positive for both.[4]

Overlap syndromes

The increased combined use of auto antibodies, liver biopsy and radiology to investigate autoimmune liver diseases has revealed a group of patients who have features of more than one autoimmune liver disease. The combinations described are those between AIH with either PBC or primary sclerosing cholangitis (PSC). The importance of recognising the overlaps lies in the implications for treatment (Table II).

The addition of immunosuppression in PSC or PBC with AIH injury or ursodeoxycholic acid to AIH with PSC or PBC features will retard the progression of disease. Vergani's paediatric work has highlighted the value of combined treatment in children with AIH-PSC overlaps. The right treatment combination retards progression and the need for liver transplantation is delayed or removed entirely.[11]

Making sense of liver-associated autoantibodies

Liver-associated autoantibodies are an integral part of the assessment of chronic hepatitis. However it is important to note that these autoantibodies can occur in other autoimmune diseases and the measured titre has no direct correlation to the severity of disease. In children lower titre levels are considered diagnostically significant. The commonly used autoantibodies that should be requested in the work-up of every patient are SMA, ANA and anti-LKM-1. These 3 antibodies will be negative in 13 - 25% of patients with disease that is typical of AIH. This proportion of patients can be reduced to less than 10% by the use of nontraditional autoantibodies such as SLA and anti-neutrophil cytoplasmic antibody (ANCA). SMA is directed against the cell's cytoskeletal proteins, particularly actin, and can be positive at low titre when there has been massive cell necrosis, in rheumatological disorders and various infections.[12] ANA are directed against nuclear targets, possibly the centromere or ribonuclear proteins, and can also be found in other diseases including drug-induced hepatitis and PSC.

TREATMENT

Immunosuppression using corticosteroids with or without azathioprine remains the mainstay of therapy. There are other aspects of treatment that are equally important in achieving good long-term success. These include counselling patients on the drugs being used, the need for treatment compliance and the lifelong nature of the disease. It is important to give attention to the prevention of bone disease, growth failure in young patients and the prevention of sepsis in the acutely ill and in cases that are difficult to treat. Patients with chronic hepatitis are at risk of developing bone disease as a result of the various effects of cirrhosis on bone and in AIH, from the long-term effects of steroid therapy. Calcium and vitamin D supplementation is therefore important. Recently vitamin K deficiency in chronic hepatitis has been shown to be a significant contributor to the development of low bone mass, and supplementation improves bone mass in chronic liver disease. Analysis of the bone mineral density scans of AIH patients at the MRC/UCT Liver Centre shows that these patients

Table III. **Indications and contraindications for treatment**

Indications	Contraindications
Clinical	Inactive cirrhosis
• Symptoms (fatigue, arthralgias, jaundice)	• No inflammatory activity on biopsy
Biochemical	Clinical
• High ALT ≥ × 10 normal	• Decompensated disease
• High ALT ≥ × 5 normal, IgG ≥ × 2 normal	• Ascites & inactive cirrhosis
Histopathology	• Encephalopathy, variceal bleeds
• Bridging necrosis or multiacinar necrosis	Known intolerance to the medication
• Interface hepatitis	• Idiosyncratic reactions

Table IV. **Treatment algorithms**

	Monotherapy	Combination therapy
Initial	• Prednisone 30 - 60 mg daily	• Prednisone 20 - 30 mg daily **and** • Azathioprine 50 - 100 mg daily
Maintenance	• Prednisone 5 - 15 mg daily **or** • Azathioprine 100 - 200 mg daily at ~ 2 mg/kg	• Prednisone 5 - 10 mg daily **and** • Azathioprine 50 - 150 mg daily
Second-line therapy	• Mycophenolate mofetil (MMF) with or without prednisone • Cyclosporin A with prednisone • Tacrolimus with prednisone • Ursodeoxycholic acid added to any of the immunosuppression combinations	

start losing bone mass well before the use of steroid therapy, starting in the hip inter-trochanteric region.[13] Growth failure is due to a combination of factors that include late diagnosis of AIH and suboptimal control of hepatic inflammation due either to non-compliance or poor management. The incidence is higher in children with hypogonadism, using high-dose steroids, and in those with another autoimmune disease such as inflammatory bowel disease and hypothyroidism.

Immunosuppressive therapy

Corticosteroids and azathioprine either alone or in combination are still the mainstay of treatment. The indications and contraindications to therapy are listed in Table III.

In cases of treatment failure, second-line agents that have been used with different levels of success include mycophenolate mofetil (MMF), cyclophosphamide, ursodeoxycholic acid, methotrexate and the calcineurin inhibitors, cyclosporine A and tacrolimus. MMF has by far the best safety profile and clinical success. In a large published series, it allowed for complete steroid withdrawal with excellent biochemical control. The side-effects that make the long-term use of the calcineurin inhibitors undesirable include hypertension, renal impairment and diabetes mellitus. However, in children, cyclosporine can be used carefully in the short term to achieve biochemical control of aggressive disease. The usual recommended treatment regimens are summarised in Table IV.

Combined therapy is preferable as it allows for the use of lower prednisone doses.

Patients presenting with fulminant liver failure are often safely and more usefully started at lower doses of steroids, (about 0.5 mg/kg body weight) as this helps to avoid the sepsis complications associated with heavy immunosuppression.

Azathioprine should be introduced as a steroid-sparing agent at about 2 weeks. Start at a low dose and increase gradually over several weeks based on the total white blood cell count (WCC) and the absolute neutrophil count. Avoid a total WCC below 3 x 10^9/l and an absolute neutrophil count below 1 x 10^9/l. Patients who have established cirrhosis with hypersplenism and low peripheral total WCC tolerate azathioprine poorly. Supplementation with folic acid at 5 - 10 mg daily is mandatory to reduce haematological intolerance.

Poor outcome during treatment is predicted by noncompliance, previous relapses, established cirrhosis at initiation of treatment, disease at a young age and HLA A1, B8, DR3 haplotype. In the absence of poor compliance, treatment failure will occur in about 15% of cases due to intolerance of steroids and azathioprine. AIH patients with fulminant liver failure who develop treatment failure should be managed in hospital as they often die from multi-organ failure and sepsis, unless offered liver transplantation. They should receive broad-spectrum antibiotic cover using a third-generation cephalosporin with ampicillin and *Candida* decontamination using oral mycostatin drops. Medrol pulses of 500 mg - 1 g IVI daily for 3 doses to try and dampen hepatic inflammation are worth trying as a first step. If this fails then second-line treatment with MMF, starting at a low dose of 250 mg po twice daily and building up to a dose of 1 g po 3 times a day over 1 or 2 weeks, will be next. Liver transplantation should be considered when heavy immunosuppression is failing and there are no clinical contraindications to transplantation.

TREATMENT WITHDRAWAL

Most patients will ask about the possibility of treatment withdrawal or at the very least steroid withdrawal. Our clinical practice is to avoid complete treatment withdrawal. Studies in which all treatment was withdrawn show significant relapse and mortality rates. Steroid withdrawal is the easier situation to deal with and should be considered in those patients where there is significant treatment intolerance or significant side-effects such as diabetes mellitus and osteoporosis. Withdrawal should ideally not be considered before the patient has achieved biochemical remission for at least 2 years on reduced doses of steroids complemented with azathioprine. When total treatment withdrawal is being considered, a liver biopsy should ideally be done first to exclude the presence of significant hepatic inflammation as there is no direct correlation between the liver enzymes and the degree of

hepatic infiltration by inflammatory cells. In the presence of significant hepatic inflammation, withdrawal would not be recommended, as the risk of relapse will be very high.

References available on request.

IN A NUTSHELL

The diagnosis of AIH is one of exclusion of other causes of chronic hepatitis. Exclude chronic viral hepatitis and where clinically appropriate, herpes simplex virus, EBV and CMV. In children and young adults remember to exclude Wilson's disease.

AIH is a frequent cause of chronic hepatitis in black Africans and the elderly and may present as an acute fulminant hepatitis.

Minimum autoantibody testing is for SMA, ANA and anti-LKM-1. The SLA is not readily available locally and the use of ANCA and AMA may be appropriate in cases suggestive of overlap syndrome. In 15% of patients, standard autoantibodies will be negative.

Treatment is lifelong, the decision to withdraw therapy involves high risk and should be a well-considered one.

Overlap syndromes should be considered in patients in whom there is biochemical evidence of bile duct injury.

Other autoimmune diseases, growth failure and low bone mass are common associations.

Liver histopathology should be supportive of AIH with a cell infiltrate of lymphocytes and plasma cells, interface hepatitis, rosetting of hepatocytes and absence of features to suggest other chronic hepatitis.