Autoimmune chronic active hepatitis

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Autoimmune chronic active hepatitis, now often referred to as simply autoimmune hepatitis has been recognised for nearly 50 years. Typically, the disease arises in a young woman who presents with an acute hepatitic illness and complains of lethargy, arthralgia, oligomenorrhoea, and fluctuating jaundice. For the purposes of clinical trials and research, guidelines for establishing the diagnosis have been published recently, but in clinical practice it is diagnosed when there is a histological picture of chronic active hepatitis together with immunological features (high levels of immunoglobulin G and serum autoantibodies) in the absence of other known causes of the histological picture. Controlled trials in the 1970s confirm the efficacy of immunosuppressive therapy in terms of improvement of both symptoms and survival. Treatment protocols based on prednisolone and azathioprine have been refined over the past 20 years so that the prognosis is now good and side effects from treatment are usually minimal.

HKMJ 1997;3:43-9

Key words: Autoimmune diseases; Autoantibodies; Hepatitis, chronic active; Hepatitis C viruses

Introduction

In the early 1950s, Waldenstrom and Kunkel, were among the first to recognise the syndrome of chronic hepatitis in young women with extreme hyperglobulinaemia.[1,2] The detection of antinuclear antibodies (ANA) and the lupus erythematosus (LE) cell phenomena in some of these patients led to the term "lupoid hepatitis", which is still widely used today.[3,4] The syndrome, however, is quite distinct from systemic lupus erythematosus (SLE) and this was reflected in the most widely used term—"autoimmune" chronic active hepatitis.[5] Most recently, it has been suggested that the name should be shortened to "autoimmune hepatitis" (AIH)[6] and it is this term that is used in this review.

The histological picture is of periportal piecemeal necrosis and prominent plasma cell infiltration of the portal tracts. These features, when present for more than six months are classified under the heading of "chronic active hepatitis" (CAH). However, such features are aetiologically heterogenous. Chronic infection with hepatitis viruses B (HBV), delta (HDV) or C (HCV) are the most clearly defined aetiologic agents but CAH is also a recognised feature of other primary liver diseases and may arise as an adverse reaction to drugs. A diagnosis of AIH implies that all of these known aetiologic factors have been excluded and that high titres of non-organ specific autoantibodies and polyclonal hyperglobulinemia are prominent.

Aetiology

Autoimmune hepatitis probably arises in a genetically susceptible host who by chance encounters the appropriate trigger. Hepatotropic viruses have been assumed to be the most likely triggers. Recently, instances of AIH development following infection with virus (HAV) have been described in patients with an antigen-specific T cell defect.[7] In others, HCV has been implicated (see below). Autoimmune hepatitis has also been recognised to follow ingestion of certain therapeutic drugs, notably oxyphenistan and methyl-dopa.[8,9] Tienilic acid (ticrynafen) may induce a specific anti-liver/kidney microsomal (LKM) antibody that leads to chronic hepatitis in up to 10% of cases.[10] As with many common autoimmune conditions, AIH is strongly associated with the HLA-A1-B8-DR3 haplotype and recent evidence suggests a secondary association with DR4 and a protective role for DR1.[11] Since DR3/DR4 heterozygotes are relatively rare in this condition it would appear that the A1-B8-DR3 haplotype and DR4 are acting independently and may identify two distinct sub-groups of the disease. In support of this contention, those with

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DR4 tend to present at an older age than do those without, and relapse on treatment less frequently. Nonetheless, only about one third of those with AIH have the HLA-A1-B8-DR3 haplotype.[11]

Mechanism of hepatocyte damage

The specific target antigen is probably the asialoglycoprotein receptor (ASGP-R).[12] In contrast to targets of the other autoantibodies in AIH it is expressed on the hepatocyte membrane[13] and thus provides an explanation for the focus of the disease in the liver. At least 90% of patients with active disease have high titres of circulating autoantibodies that react with ASGP-R.[14] Most also have antigen-specific T cells (predominantly of the CD4 helper/induced subset), sensitised to ASGP-R, which can be isolated from the liver of AIH patients.[15,16] Tissue damage is probably mediated by antibody-dependent cellular cytotoxicity in which ASGP-R antibodies and non-T (K) cells cooperate.[17] There may be an additional non-antigen–specific suppressor cell defect, linked to the HLA-A1-B8-DR3 haplotype. It is this lesion that can be overcome by immunosuppressive therapy.[18]

The role of hepatitis C virus infection

A test for antibodies to HCV became available towards the end of 1989 and led to reports that nearly 50% of patients categorised as having Type I AIH, and an even greater percentage of those with Type 2, tested positive for anti-HCV.[19] In fact, many of these were "false positive" results and the application of more specific tests revealed positive results in fewer than 10% of British and North American cases.[19-22] However, when the same specific tests were applied to patients from Italy, a high percentage remained strongly positive, particularly those with Type 2 disease.[21] The implications of these findings for treatment remain unclear. In this rapidly changing field, a clinician faced with an anti-HCV positive patient who otherwise appears to suffer from AIH, should take advice from a specialist unit before beginning either immunosuppressive or antiviral therapy.

The difficulties in distinguishing between AIH and chronic HCV infection using autoantibodies, and the varying reports of the effectiveness of various treatments, highlighted just how variable were the criteria being used for the diagnosis of AIH. It also emphasised problems in defining precisely what was meant by the terms response and relapse in relation to immunosuppressive therapy. This led to the formation of an International Autoimmune Hepatitis Group that met for the first time in Brighton, United Kingdom, in 1992, to reach a consensus on these matters. In a subsequent publication detailed criteria were laid down to define the terms diagnosis, response, and relapse.[6] It is anticipated that these criteria will be used mainly in a research setting so that clinical trials from different areas of the world can be readily compared.

The clinical syndromes

Classical autoimmune hepatitis

Previously termed Type 1, this type corresponds closely to the initial description of "lupoid" hepatitis. The patient is usually a young woman who presents with an acute hepatitic or a chronic, rumbling illness. Clinical features include lethargy, arthralgia, oligomenorrhoea, fluctuating jaundice, and a Cushingoid appearance with striae, hirsutism, and acne. Cutaneous manifestations of chronic liver disease and signs of cirrhosis (which may be present at presentation, or may develop during the disease) may be prominent. "Autoimmune" diseases such as hyperthyroidism and Coomb's positive haemolytic anaemia may also be present. The response to corticosteroid therapy is often used as one of the diagnostic criteria. Moderate doses of prednisolone result in the disappearance of symptoms and normalisation of liver biochemistry but a relapse is usually rapid when treatment is stopped. Nowadays, this "classical" form of the disease represents a smaller proportion of AIH cases.

Autoimmune chronic active hepatitis with anti-liver/kidney microsomal antibodies present

The presence of circulating anti-liver/kidney microsome antibody Type 1 (anti-LKM1) has been used to define a separate subgroup of AIH, "Type 2".[23] This group of antibodies, first described by Rizetto and colleagues in 1973, comprise a group of at least three distinct antibodies. Anti-LKM-1 reacts with cytochrome P450db1 (now termed P450 IID6),[24] while anti-LKM-2 (associated with tienilic acid-induced hepatitis) reacts with cytochrome P450-8,[10] and anti-LKM-3 (found in about 10% of chronic Delta virus infections) recognizes a third, yet unidentified, microsomal antigen.[25] Positive cases are less frequent than ANA/SMA-positive AIH and have been described most often in continental Europe. The disease in many respects is like "classical" AIH, with a marked female predominance, a bimodal age distribution, hypergammaglobulinaemia, and steroid sensitivity. On the other hand, distinctive features include a tendency to present in the paediatric age group[26] and a more common association with other autoimmune disorders such as insulin-dependent diabetes mellitus, autoimmune thyroid disease, and vitiligo. The presentation may be fulminant, with marked his-

Table. Causes of, and diseases associated with, chronic active hepatitis. Reactions associated with therapeutic drugs closely resemble, and are sometimes categorised with, the autoimmune type. *The distinction between autoimmune and cryptogenic types is not always made.

Hepatitis B virus and delta infection
Non-A Non-B viral infections, including hepatitis C
Wilson's disease
Alcoholic liver disease
Alpha-1 antitrypsin deficiency
Drugs - alphamethyl dopa - oxyphenisitan - nitrofurantoin - isoniazid - tienilic acid
Autoimmune Type 1 Type 2
Cryptogenic*

tological features and a propensity to progress rapidly to cirrhosis.

Other presentations

Auto-immune hepatitis is increasingly being diagnosed in older patients. Their disease broadly conforms with "classical" AIH but also affects males more often.[27] The most common presenting symptoms are profound lethargy, epigastric pain, and fluctuating (often mild) jaundice. Anti-nuclear antibody, smooth muscle antibodies (SMA) and antimitochondrial antibodies (AMA) are found as frequently as in the younger age group, but the hyperglobulinaemia tends to be less marked and aminotransferase activities may be only moderately (5-10 fold) elevated. In all other respects, however, their disease is indistinguishable from that seen in younger patients. The usual presentation, with either chronic or acute disease, has been described above. Secondly, and most importantly, it is increasingly recognised that many patients with AIH may be asymptomatic for long periods. Manns et al describe a new subgroup of AIH characterised by the presence of antibodies, detectable only by radioimmunoassay, against a soluble liver antigen (SLA) although these findings have yet to be confirmed by other laboratories.[28]

Some patients with "cryptogenic" CAH (i.e. no aetiological factors and seronegative results for ANA, SMA, and LKM are, in all respects—characteristic histology, high serum gammaglobulin and IgG concentrations, complete sensitivity to corticosteroids—other than their autoantibody status, similar to those classified as "autoimmune".[29,30] Such patients have either never had autoantibodies or lost them during a prolonged asymptomatic phase. In support of this latter contention, cryptogenic patients are on average, 10 years older and have a much higher frequency of cirrhosis at presentation, but they still have anti-liver specific membrane lipoprotein (anti-LSP) and anti-ASGP-R antibodies at titres similar to those found in patients with classical AIH.[29,30]

Diagnosis

Laboratory investigations reveal hepatitic features with aspartate aminotransferase activity that is more than 10 times greater than the upper limit of the reference range. The g-globulin concentration is grossly raised (often in the range of 50-100 g/L) and is mainly polyclonal immunoglobulin G in nature. Anti-nuclear antibodies are found in the sera of approximately 70% of cases, many of whom, together with the remaining 30%, have SMA; AMA are detectable in about 15%. The diagnosis cannot be firmly established without a liver biopsy being done for histological examination. However, when the prothrombin time is prolonged and cannot be corrected, it may be necessary to institute treatment before biopsy or to use the transjugular approach.

Due to the widespread availability of autoanalysers to measure liver function tests many patients are diagnosed before they develop symptoms. In a study of 47 asymptomatic patients with chronic elevations of AST, 34 had histological features of CAH and 18 of these were ultimately classified as autoimmune. Furthermore, 10 had already reached the stage of cirrhosis, which implies prolonged chronicity.[31] This is in agreement with the common finding that even asymptomatic patients are often cirrhotic at presentation.

The detection of ANAs are a useful diagnostic marker for AIH but they are also found in other liver disorders. The ANAs give a homogeneous pattern of immunofluorescent staining on tissue section, similar to that seen with ANA in patients with SLE and, as with the latter, are usually associated with serum auto-

antibodies against double-stranded DNA (dsDNA), but they react with a different antigen to that recognized by anti-dsDNA in SLE. High titres (> 1:80) of IgG class SMA with anti-actin specificity are particularly associated with AIH. Anti-ASGP-R is more often associated with CAH[14,32] and also correlates with severity of periportal inflammation and piecemeal necrosis, occurring infrequently in other liver disorders.

Differential diagnosis

All the factors listed in the Table need to be excluded. This involves a screen for hepatitis viruses B, C, and D, and the taking of a careful drug and alcohol history. It is crucially important to rule out Wilson's disease in any young person presenting with features characteristic of CAH. This should include, at a minimum, estimation of serum caeruloplasmin, serum copper, and examination of the eyes for Kayser-Fleisher rings. The serum concentration of α-1-antitrypsin should also be measured together with the phenotype if available.

Overlap with other conditions

The distinction between CAH and primary biliary cirrhosis is not always clear and the histological, clinical, and immunological overlap has been well described. Many children with florid anti-actin positive AIH ultimately progress to primary sclerosing cholangitis and the same progression has also been noted in some young adults.[33] Patients with well documented Wilson's disease may develop very high titres of SMA and ANA. Very recently, the development of autoantibodies in patients with HCV treated with interferon has been reported, suggesting that these were cases of autoantibody-negative AIH whose disease was unmasked by this immunomodulatory therapy.[34]

Natural history of autoimmune chronic active hepatitis

Early studies emphasised the serious, invariably fatal, nature of the disease and the prognosis was also grave among patients in the untreated arm of three controlled clinical trials of immunosuppressive therapy reported in the 1970s. In the Royal Free Hospital trial, 62% were dead within a mean follow up period of four years and in the Mayo Clinic trial the figure was 50% at two years.[35,36] As already noted, patients with very mild disease are now detected more frequently and while those with severe disease still have a poor outlook without treatment, the prognosis of the whole group is probably not as poor as initially reported.

In the absence of cirrhosis, piecemeal necrosis (the hallmark of the disease) appears to be a relatively benign feature that seldom progresses to cirrhosis. By contrast, patients in the group with both piecemeal and bridging necrosis present frequently progress to cirrhosis.[37] Many workers consider that since piecemeal necrosis on its own is a relatively benign lesion, treatment should be confined to those with bridging necrosis and/or cirrhosis. There is also a general feeling that those patients in the trials that showed efficacy of corticosteroid therapy were a highly selected group from referral centres who had advanced and severe disease. On the other hand, given the fluctuating nature of the illness and the possibility that it may, at any time become more severe, early intervention with corticosteroid therapy would seem sensible and may partly account for the improved survival seen since the early 1970s. The extent to which corticosteroid therapy can ameliorate symptoms, irrespective of any prolongation of survival, should also not be underestimated.

Treatment

Without treatment, AIH has a high mortality rate. Three controlled studies have established that corticosteroid therapy induces and maintains histological remission and improves symptoms and survival[35,36,38] at least among those with severe forms of the disease. Azathioprine alone is not effective in inducing remission but is of proven value in decreasing the dose of prednisolone required to maintain remission.[36,38,39] Subsequent withdrawal of all immunosuppressive treatment[40] or azathioprine[41] is associated with relapse in most cases. In 1988 it was shown that once prolonged remission has been induced with corticosteroids, the corticosteroid element could be withdrawn completely and remission maintained by azathioprine alone, provided that a high dose (2 mg/kg/day) is used.[42] Although there were no serious short term side effects, concern was expressed about the long term effects of this high dose azathioprine regimen. Long term follow up suggests, however, that this form of treatment is safe. The opportunity to withdraw corticosteroids is particularly important in those who suffer severe Cushingoid side effects and may reduce the long term side effects of steroids, including osteoporosis.[43]

Management approach

The management approach is outlined in the Figure. If the patient is symptomatic, has histological evidence of bridging necrosis, an aminotransferase activity of greater than 10 times the upper limit of reference or is jaundiced, then immunosuppressive therapy is clearly indicated. Under these circumstances, a prompt resolution of symptoms and improvement of histological features may be anticipated and there is good evidence

that survival is markedly prolonged. On the other hand, if the patient is asymptomatic, with no histological evidence of bridging necrosis and only mildly abnormal liver function tests, the decision whether or not to use immunosuppressive treatment is more difficult. Most units will, on the basis of the arguments outlined above, treat both groups of patients similarly, while awaiting the results of clinical trials that address the problem of optimal management of mild disease.

The standard approach is to induce remission with prednisolone, using 0.5 mg/kg body weight; higher doses are seldom required. When the aminotransferase level has fallen to less than twice the upper limit of the reference range (usually after 2-8 weeks) the dose of prednisolone is decreased to 0.25 mg/kg and azathioprine to 1 mg/kg is added. Azathioprine is used as a steroid-sparing agent; it has no role in the induction of remission. The aim should be to maintain the aminotransferase levels within the reference range and once this has been achieved, 5 to 10 mg prednisolone and 50 to 75 mg azathioprine is a typical regimen. The dosages should be kept constant for a minimum of two years and not further titrated. Aminotransferase activity is not an infallible method of assessing disease activity and a liver biopsy should be undertaken when biochemical remission has been obtained to confirm histological remission.

Even after two years of remission, attempts to withdraw corticosteroid therapy are invariably unsuccessful. The resulting relapse can be dangerous if liver function tests are not monitored very closely and treatment reinstituted before symptoms recur. It is usually possible to withdraw the corticosteroid component, after prolonged remission, if the dose of azathioprine is increased from 1 mg/kg to 2 mg/kg/day. This approach is probably particularly useful in those patients in whom corticosteroid side effects are prominent. Frequent measurement of platelet and white cell counts are important when high doses of azathioprine are used, particularly over the first six months. In response to a marked fall in these parameters (to below the pre-treatment values), the azathioprine dose should be reduced to 1 mg/kg or withdrawn completely, but low stable levels may reflect hypersplenism and in this situation the high dose azathioprine can be continued. After many years, the disease does enter a "burnt-out" phase when all treatment can be withdrawn, but patients should still be checked at least at yearly intervals, as relapses can occur at any time over the next 10 years.

Corticosteroid insensitivity

Approximately 10% of patients never achieve a remission with corticosteroids and a smaller percentage become unresponsive after an initial response. Occasionally, remission can be induced by high dose corticosteroid therapy (prednisolone, 1 mg/kg/day) but more often there is progressive liver failure and early referral to a liver transplant unit is indicated.

Prognosis and survival

In a large retrospective analysis of patients with AIH, all of whom received immunosuppressive therapy, the overall five-year survival was 85%.[29] Those with cirrhosis had a significantly worse prognosis. Patients who were anti-LKM antibody positive were also reported to have a poorer prognosis[25] but this is probably accounted for by the high frequency of cirrhosis in this group.

Causes of death

Other than incidental, non-hepatic causes, death is now largely a consequence of cirrhosis. In the small group of steroid-resistant cases, and the few who present with fulminating disease, death may be due to acute hepatic failure and its complications—although liver transplantation is increasingly becoming a life-saving option in these cases. For the majority, hepatocellular failure secondary to cirrhosis is the major cause of death, followed by variceal haemorrhage, septic complications, and hepatocellular carcinoma.

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Fig. Current management of patients with autoimmune hepatitis. 1) Histological confirmation of the diagnosis may need to await normalisation of the prothrombin time or be obtained by the transjugular approach. 2) Doses of prednisolone of >30 mg/day are seldom indicated. 3) Many patients are leucopaenic before treatment with azathioprine because of hypersplenism. It is a falling white cell count or platelet count rather than an absolute leucopaenia (or thrombocytopaenia) that is the indication for reduction or withdrawal of the drug. 4) Relapse is arbitrarily defined as an AST activity more than three times the upper limit of normal. Relapse is unusual at other stages in management but also requires re-introduction of corticosteroids. Reproduced with permission of Gut. Taken from: Johnson PJ, McFarlane IG. Gut 1991;(Suppl):63S-72S.