The relationship between autoimmune markers and different clinical syndromes in autoimmune hepatitis

Autoimmune hepatitis (AIH) is a disease of unknown aetiology but is presumed to have a basis in aberrant autoreactivity. It is characterised by hypergamaglobulinaemia due mainly to selective elevation of serum IgG, a wide range of circulating tissue autoantibodies, an association with other autoimmune disorders (particularly thyroid disease) in the patients or their first degree relatives, a picture of periportal (interface) hepatitis on liver biopsy with a predominantly lymphoplasmacytic necroinflammatory infiltrate without cholangiolic or other changes normally associated with liver diseases of other aetiologies, and usually a notable response to immunosuppressive therapy. In common with other autoimmune diseases, it is also associated with inheritance of the HLA B8-DR3 haplotype and, particularly, with the DR3 and DR4 allotypes. Diagnosis is based on the combination of these features together with careful exclusion of all other possible causes of liver disease.

AIH is notably heterogeneous with respect to its presentation, severity and outcome. Presenting features vary from completely asymptomatic (the disease being revealed at routine health screening), through an insidious onset with signs and symptoms fluctuating with a periodicity of anything from a few months to one or two years, to a severe acute (occasionally fulminant) hepatitis that can be difficult to distinguish clinically from acute viral hepatitis. Although women predominate (4:1) it also affects men and it may present at any age—with two peaks of onset: peripubertally and between the fourth and sixth decades of life (fig 1). Younger patients usually have quite severe disease that can sometimes be difficult to control while older patients tend to have a less severe form.

During the past 10 years attempts have been made to classify AIH according to various parameters with a view to defining relatively homogeneous groups of patients with features that might be useful for assessing prognosis and planning treatment strategies. Biochemical liver tests are not very useful discriminators in this regard. Although these typically show a “hepatitic” pattern of abnormalities, serum aminotransferase activities and bilirubin concentrations vary widely—from very mildly abnormal to more than 50 times the upper normal limits—even within a relatively homogeneous population of patients with histologically severe disease. Efforts have therefore concentrated on classifying patients according to autoantibody profiles and/or different immunogenetic markers. This is, however, a controversial area—with some authorities recommending various subdivisions of AIH along these lines and others, including a number of international working parties, finding it difficult to endorse them.

**Autoantibodies in AIH**

The autoantibodies that are typically associated with AIH are those that react with nuclear and smooth muscle components. The antinuclear antibodies (ANA) are most commonly directed at DNA and histones and give the so called “homogeneous” pattern of immunofluorescent staining of nuclei, similar to that seen with ANA in patients with systemic lupus erythematosus. Other reactivities giving different staining patterns (perinuclear, speckled, nucleolar) are also frequently seen but the different patterns seem to have no practical clinical implications.

The smooth muscle antibodies (SMA) react with a variety of cytoskeletal components including F-actin, myosin, desmin, vimentin, and tubulin. Some authorities are of the opinion that high titre antiactin antibodies are specific for AIH but others have drawn attention to the fact that antiactin occurs in other diseases and, furthermore, is found in only about 50% of patients with AIH with high titre SMA. This debate is fuelled by recognition that the method of detection may be crucial and that reliance on antiactin specificity can lead to missed diagnoses in patients with AIH.

A third autoantibody, designated type 1 liver-kidney microsomal antibody (LKM-1), is also well recognised in association with AIH. LKM-1 is distinguished from other liver-kidney microsomal antibodies by its specificity for the

![Figure 1: Distribution according to age at presentation and HLA DR3 and DR4 status of 118 adults with autoimmune hepatitis attending the Institute of Liver Studies, King's College Hospital, London, UK.](http://gut.bmj.com/)

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cytochrome isoform P450IID6. Overall, in most large series, patients presenting with ANA and/or SMA account for about 80% of cases of AIH whereas LKM-1 occurs in only about 3–4%—usually young women with severe disease without ANA or SMA.

In addition to these “conventional” autoantibodies, so-called because they are routinely determined by most clinical immunology laboratories, patients with AIH have a wide range of other autoantibodies. Those most frequently found include perinuclear staining antineutrophil cytoplasmic antibodies (pANCA), and antibodies reacting with the hepatic asialoglycoprotein receptor (ASGP-R) and with a soluble liver antigen (SLA). Some of these occur in almost all patients with active disease, or without the conventional autoantibodies. Two other autoantibodies that have received recent attention but occur much less frequently are: anti-LC1, which reacts with a liver specific cytosolic antigen and anti-LP which recognises a cytosplasmic antigen shared by liver and pancreas.

**Immunogenetics of AIH**

The association of AIH with inheritance of the HLA DR3 allotype in caucasioids has long been recognised. The secondary association with DR4 (in DR3 negative patients) has been more recently defined. DR3 tends to occur more frequently in younger patients with severe disease whereas DR4 is mostly associated with an older age at presentation and with generally milder disease that is easier to control (fig 1). Interestingly, in Japan, where DR3 is very rare in the normal population, the primary HLA association is with DR4 and almost all patients are in the older age groups, with a peak onset at 50–60 years of age. Since DR3 and DR4 are seldom inherited together as a haplotype in AIH, this apparent segregation of these two allotypes with age at presentation and severity of disease suggests that there may be two genetically distinct populations of patients with AIH. A further possible genetic subdivision (within the DR3 positive group) is suggested by the finding of a significantly increased frequency of HLA B14 and of the silent complement gene C4A-Q0 in patients with LKM-1 antibodies. Possession of C4A-Q0 is not, however, confined to this group. It is also found in a high proportion of patients with ANA/SMA positive AIH.

**AIH and hepatitis C virus infection**

Following the identification of the hepatitis C virus (HCV) in 1989, reports began to appear from Spain and Italy that a high proportion of patients who otherwise fulfilled criteria for AIH had evidence of HCV infection, suggesting that this virus might be an aetiological factor in the development of AIH. This has been the subject of much debate, which has tended to concentrate on the association of LKM antibodies with HCV infection and about which more than 70 papers have been published in the past five years—somewhat overshadowing the fact that HCV infection is found almost as frequently in AIH patients with ANA and/or SMA in these countries. It was soon recognised that, in contrast to the typical LKM positive AIH patient, these patients tended to be older, were usually men and had lower LKM antibody titres, and it was subsequently found that the LKM antibodies in patients with HCV infection often do not recognise the same epitopes on cytochrome P450IID6 as LKM-1 antibodies in patients with AIH. A comprehensive discussion of HCV infection in AIH and of the prevalence and significance of autoantibodies in patients with chronic hepatitis C is beyond the scope of this article. Suffice it to say that the LKM/HCV association seems to be peculiar to southern Europe—HCV infections in patients with AIH or LKM antibodies in patients with HCV being very rare in northern Europe and North America. It is noteworthy, however, that although there is a high frequency of HCV infection in southern Europeans presenting with LKM antibodies, the prevalence of LKM in patients presenting with HCV in these areas is only about 6%. The LKM/HCV association is simply a result of the high background prevalence of HCV in southern Europe because in countries with a similar HCV prevalence, such as Japan and Turkey, LKM antibodies in patients with HCV are rare. Thus it seems that there may be important genetic differences between patient populations that we do not yet understand.

**Subtypes of AIH**

The first formal proposals to distinguish between different subgroups of AIH came in 1987. Homberg and colleagues noted that patients with AIH with LKM-1 antibodies are almost always young women with severe liver disease associated with a higher frequency of other autoimmune disorders (particularly insulin dependent diabetes, vitiligo, glomerulonephritis, and autoimmune haemolytic anaemia) than those with antiactin antibodies, which were very rare in their LKM-1 positive cases. They proposed that classic (ANA/SMA positive) AIH should be designated as type 1 and patients with LKM-1 should be classified as having type 2 disease. They also reported the finding of antibodies against the liver specific cytosolic antigen, LC1, in a small group of patients who were either seronegative for all of the conventional autoantibodies or had only LKM-1 and suggested that anti-LC1 could be used as an additional marker of type 2 AIH. At about the same time, Manz and coworkers’ reported that the approximately 20% of patients who were seronegative for the conventional autoantibodies (but otherwise fulfilled criteria for AIH) when they first presented frequently have SLA antibodies and suggested that they should be designated as type 3 AIH—defined by anti-SLA positivity.

The discovery that in southern Europe many patients with presumed AIH have evidence of exposure to HCV (see earlier) presented a problem for differential diagnosis, particularly of type 2 AIH from HCV infection. Homberg’s group proposed that type 2 should be subdivided into: type 2a, young (HCV negative) women with severe disease and high titres of LKM-1, and type 2b, older, predominantly male (HCV positive) patients with low LKM-1 titres. They further suggested that anti-LC1 positivity could be used to distinguish between these types but this has since been disputed by Lenzì and colleagues and others have concluded that anti-LC1 does not identify a distinct disease subset.

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<th>Table 1</th>
<th>Summary of proposals for classification of autoimmune hepatitis according to serum autoantibody profiles</th>
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<td><strong>Type and subtype</strong></td>
<td><strong>Main defining feature</strong></td>
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ANA, antinuclear antibody; SMA, smooth muscle antibody; LKM-1, liver-kidney microsomal antibody type 1; HCV, hepatitis C virus; LC1, liver cytosolic antigen; SLA, soluble liver antigen; LP, liver-pancreas antigen; ASGP-R, asialoglycoprotein receptor.
In 1993, on the basis of a study of anti-liver-pancreas (anti-LP) and other autoantibodies in a large group of patients and control subjects, Stechemesser and colleagues advanced an alternative classification: type 1a, “lupoid” hepatitis (ANA positive ± antiactin antibodies); type 1b, only antiactin positive; type 2, LKM-1 positive; and type 3, anti-LP positive (± other autoantibodies). Amalgamation of these with all of the other proposals above gives rise to a total of six possible subtypes of AIH: 1a, 1b, 2a, 2b, 3a, and 3b (table 1). For completeness, at least two other subtypes have to be included, to account for patients who are seronegative for ANA but have SMAs that do not react with actin (type 1c) and patients who are seronegative for all of these autoantibodies but may have anti-ASGP-R antibodies (type 3c).

To date, only the broad subdivision into types 1 and 2 has received some degree of general acceptance. Improvements in diagnostic tests for, and increased knowledge about, HCV infection have largely rendered the subdivision of type 2 unnecessary. The classification of type 3 based on anti-SLA positivity in the absence of conventional autoantibodies was promulgated with enthusiasm for a time by some authorities in the field, but it is now considered that anti-SLA is not specific for this subgroup, most of whom are also seropositive for anti-ASGP-R. The multiple subdivisions proposed by Stechemesser et al have also not been widely adopted.

**Clinical utility of subtyping AIH**

Subclassification of a heterogeneous disorder such as AIH can facilitate diagnosis and clinical management through focusing investigations and accurately defining prognosis. To be really useful, however, any such classification needs to be exclusive, universally agreed and applicable (with confidence) to the individual patient seen in the clinic. None of the subtypes of AIH that have been proposed entirely fulfill these criteria and there are inherent dangers in attaching labels to groups of patients when these conditions are not met. For example, although there may be some justification for defining type 2 AIH on the basis of a unique autoantibody profile and a significant association with HLA B14, on their own these two criteria have little clinical utility. The clinical relevance comes from the supplementary criteria that it is usually a severe disease which is difficult to control and primarily affects young women with a higher frequency of concomitant non-hepatic autoimmune disorders than other patients with AIH. But these additional criteria are not exclusive. If they were, then by definition type 1 should be a milder disease affecting older subjects with a better prognosis, which is not the case. As noted above, type 2 comprises a very small proportion of all cases of AIH. The large majority of young women with severe disease are type 1, and the frequency of other autoimmune diseases in this group, although lower than in type 2, is not significantly so. Furthermore, there is still no concrete evidence that type 2 defines a distinct population on the basis of aetiology or pathogenesis and most patients in all of the proposed subgroups respond to immunosuppressive therapy. Indeed, the response is so striking that an international panel was recently prompted to include it as part of the definition of AIH.

Age at presentation is clearly an important factor. Young patients (male or female), irrespective of their autoantibody profiles, usually have more severe disease than patients who present later in life. Most do respond to therapy, but they tend to require somewhat higher doses for longer periods and relapse more frequently than the older patients. Thus a simpler, and arguably more practical, classification could be based on age at presentation. However, this may be too simplistic and, again, it is not exclusive because older patients can also have severe disease that can be difficult to control. The discriminating factor seems to be the immunogenetic background—that is, patients with HLA DR3 have more severe liver disease. As younger patients are predominantly DR3 positive it is perhaps not surprising that, as a group, they usually have more severe disease. Much progress has recently been made, by molecular genotyping, in defining alleles that confer susceptibility or resistance to AIH, but there is still a long way to go. In the meantime, although the DR3 and DR4 allotypes are not diagnostic for AIH, they would seem to provide a more logical, and clinically useful, basis for subdivision of the disease.

Finally, there is the question of the 20% or so of patients who present without the conventional autoantibodies. In many, the autoantibodies appear later in the course of the disease (especially during relapses) but the initial diagnosis can be difficult. Most such ANA/SMALKM seronegative cases will have a number of other autoimmune syndromes, particularly anti-ASGP-R and anti-SLA, but these tests for most of these are not yet commercially available and are currently performed in only a few specialised laboratories. In these cases the diagnosis is usually made on the basis of the combination of a “hepatic” pattern of serum biochemical abnormalities, elevated serum IgG, typical histological findings, immunogenetic background (a history of other autoimmune diseases in the patient or first degree relatives and HLA typing), and careful exclusion of other causes of liver disease. Such patients are indistinguishable from ANA/SMALKM positive cases with respect to variability in severity of disease, response to treatment or prognosis and there therefore seems to be little justification at present for separately classifying them as type 3 AIH.

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